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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

SEPTEMBER, 1926

ORIGINAL ARTICLES.

PANCREATIC CYSTS, WITH THE REPORT OF SEVEN CASES.*

By Julius Friedenwald, M.D.,
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Pancreatic cysts are rather uncommon, but are nevertheless of sufficient frequency to enter into consideration in the diagnosis of obscure conditions of the upper abdomen in as much as they not uncommonly simulate other affections. Their rarity is revealed by the fact, that Hale White[1] observed but 4 cases in nearly 6000 autopsies performed at Guy's Hospital from 1883 to 1894. According to Mayo Robson and Cammidge[2] but 175 cases have been recorded up to 1907, while Körte[3] collected 177 up to 1902.

Bozeman[4] 1882, was the first to extirpate a pancreatic cyst successfully, and since then similar successes have been recorded by Zweifel,[5] Körte,[6] Willis and Budd,[7] McCann,[8] Moschcowitz,[9] Roic,[10] de Francisco,[11] Goebel,[12] Alexandrow,[13] and others.

Gussenbauer[14] first called attention to the diagnostic importance of this condition, and advised drainage as a correct method of surgical procedure. An important contribution in this country is found in the report of an interesting case of multilocular cystoma of the pancreas by R. H. Fitz[15] in 1890.

Case Reports. There were 7 cases of pancreatic cysts in our series. The following histories present their most important features:

* Presented at the Meeting of the Association of American Physicians at Atlantic City, May 5, 1926.

CASE I.—*Pancreatic cyst of several years duration; operation with relief for over a year followed by death after two years due to malignant degeneration.*

F. A., female, aged fifty years, had enjoyed good health until about three years previous to seeking medical advice (February 15, 1904). She then noted a gradual swelling in the upper abdomen with occasional attacks of abdominal colic, appearing at first at long and irregular intervals. These attacks were accompanied with abdominal distention, nausea and vomiting and lasted from three to five hours.

On examination the heart and lungs were found normal. In the upper abdomen a mass was easily palpable, which gave every evidence of being cystic in nature. The tumor was very large, occupying the greater part of the upper abdomen, situated however somewhat more to the right with the stomach displaced above it and surrounded by an area of tympany. The diagnosis of pancreatic cyst was arrived at and operation was performed by Dr. Howard A. Kelly. A median incision was made with a view of extirpation, but it was found that the main part of the tumor lay too near the head of the pancreas to permit complete excision. The cyst was therefore drained of a large quantity of light, somewhat chocolate-colored viscid fluid, containing cholesterin crystals, epithelial cells as well as red and white corpuscles. Drainage was maintained for some weeks until the discharge had dwindled away to a small negligible amount. The fistula finally closed entirely after several months. The patient remained well until January, 1906. She began again to suffer with abdominal distress, nausea, vomiting and in a short time lost 20 pounds in weight. Her urine then began to show the presence of sugar and the patient was treated for diabetes. On further investigation however, the presence of sugar in the urine was noted only at irregular intervals. The stools were soft and large in amount and fatty. Jaundice soon developed and a large mass the size of an infant's head manifested itself in the upper abdomen, the center of the tumor being located beneath the line of the incision. The mass was hard and nodular. The liver soon became enlarged and also nodulated. Further loss of flesh was noted, nausea and vomiting were profuse, and the patient became cachectic and died on April 26, 1906. Death was evidently due to a malignant degeneration of the cyst with secondary involvement of the head of the pancreas and the liver.

CASE II.—*Pancreatic cyst probably of three years standing; evidently produced by trauma; causing violent abdominal colic; operation; recovery.*

J. K., male, aged fifty-six years, was admitted to the Mercy Hospital, December 12, 1906, complaining of attacks of severe abdominal colic. He gave a history of attacks of a similar type since June, 1903, following a severe blow upon the abdomen. At first these appeared at irregular intervals, often many months apart, but during the past six months had become more intense, and occurred at periods of two to three weeks and would last from one to three days. They had been variously diagnosed as renal and biliary in origin. The last attack which forced the patient to seek entrance into the hospital began a day ago with pain in the upper abdomen, radiating to the left hypochondrium, and into the left abdomen. It was so intense that several hypodermic injections of morphin were required before relief was afforded. There was much nausea and occasional vomiting. The bowels were constipated.

On physical examination the patient showed evidence of loss of flesh and weakness; there was no rise in temperature. The chest organs were normal. The abdomen was much distended, and there was tenderness over the entire upper area. A mass was easily palpable, extending from the mid-epigastrium into the left hypochondrium and lumbar region. Its surface was smooth, and there was no evidence of fluid beneath. The edge of the

liver was just palpable under the right costal arch, and the spleen and kidneys could not be felt. The blood examination showed 70 per cent of hemoglobin; 4,720,000 red cells; 5800 leukocytes. The differential count was normal. The urine was normal. The impression obtained was that we were dealing with a possible pancreatic cyst on account of the location of the mass, and the attacks of colicky pain following trauma three years previously although the presence of a mass associated with the left kidney could not be entirely ruled out. Operation was performed by the late Dr. J. W. Chambers on the following day. A left rectus incision was made, and a large cyst was discovered, which had pushed the stomach up and the transverse colon down. The cyst was exposed, and 2500 cc. of a dark colored fluid were evacuated by puncture. The edges of the cyst wall were sutured to the abdominal peritoneum, the interior of the cyst thoroughly cleansed and drained. The material contained cholesterin crystals, fat globules, epithelial and blood cells.

The patient made an uneventful recovery, and was discharged from the hospital in three weeks following operation with a small sinus discharging a clear fluid. When the patient was examined a year later the sinus had closed and he appeared to be in good health.

CASE III.—*Pancreatic cyst developing within three months following removal of gall stones; drainage and partial removal of cyst; patient well after thirteen years.*

M. M., female, married, aged forty-nine years, was admitted to the hospital on October 29, 1912, as an emergency case. She gave a history of not having been well for the past three or four years, and had complained of pain in the upper right quadrant of the abdomen, with indigestion. For the past two or three weeks this pain had been so excessive as to require morphin for relief.

Her past history was negative as to typhoid fever.

On physical examination her heart and lungs were found normal. The abdomen was tense, but the liver could be easily palpated, reaching three-fingers breadth below the costal margin. Its surface was smooth, but painful on pressure. The temperature registered 102.5, and the leukocytes numbered 44,000. Immediate exploration was insisted on.

Operation (Cullen): A right rectus incision was made. The gall bladder was exceedingly small and contained numerous yellowish-white facetted stones. The wall of the gall bladder was about 2 mm. thick. The gall bladder was drained. The patient's recovery was rather slow and during her convalescence she complained of considerable pain in the back, which seemed almost uncontrollable. She also had pain in the epigastrium and in the right hypochondriac region. A mass was now felt in the left upper abdomen which extended well downward below the umbilicus and across the median line, merging with the liver dullness. It was not nodular but was tender on pressure. The patient left the hospital December 6, 1912, but returned on December 31, 1912, complaining of great pain in the left upper abdomen and back, which was somewhat relieved by reclining forward. There was considerable indigestion present, and almost constant vomiting. She had lost her appetite and complained of shortness of breath and palpitation. There was no rise in temperature and no increased leukocytosis. The abdomen was very prominent in its upper area and the superficial veins were distended. A mass could be detected in the epigastrium which was definitely pulsating, but not expansile. It moved on respiration and extended to the right almost to the hypochondrium, and was continuous with the liver dullness and to the left with the splenic dullness. It was tender to pressure. The presence of a pancreatic cyst was held in mind.

At exploratory operation an opening was made between the stomach and transverse colon and when the lesser peritoneal cavity was entered, the tumor was encountered. It was found to extend to the left toward the spleen, and on the right beneath the liver, below it passed downward toward the pelvic brim. After introducing a needle into the mass, a quantity of whitish fluid was obtained which at once revealed the presence of a pancreatic cyst; a trocar was next introduced and several liters of this fluid removed. As it flowed out one could distinguish the presence of cholesterin crystals on the surface of the fluid. The walls of the cyst varied from 2 to 3 mm. in thickness. After as much of the fluid as possible had been discharged, the edge of the sac was stitched to the skin at the lower angle of the incision. The patient stood the operation well, gradually improved, and was discharged on February 5, 1913.

On histologic examination, the cyst was found to be composed of fibrous tissue. There was no evidence of any epithelial lining.

The patient has been seen on various occasions since the operation and, aside from a hernial protrusion corresponding to the point where the drains were inserted, is quite well. There is no evidence at present of any cyst or any thickening.

CASE IV.—*Drainage of pancreatic cyst of over six years duration; second operation for drainage and partial removal of cyst about six and a half years later.*

G. P., female, married, aged twenty-nine years, was admitted to the hospital, July 8, 1918 with the complaint of a painless lump in her left upper abdomen which was first noted over six years ago. It was then the size of an orange. The patient has always been well otherwise.

On physical examination the patient was found fairly well nourished, rather pale, and weighed 123 pounds. The thoracic organs were normal. The abdomen was slightly distended, soft, but asymetrical. Occupying the left side of the abdomen was a mass. It had its origin beneath the costal margin on the left, extending over to the median line and to the umbilicus and occupied almost the entire left upper abdomen. At the median line its edges were rather rounded; below it was also round. By pressing upward it could be carried up to the edge of the costal margin of the right side. By pressure beneath the costal margin on the left the tumor could be carried down to the pelvic brim. In other words it was relatively freely movable. The diagnosis naturally lay between kidney and spleen, though ovarian cyst had also to be taken into consideration. A pelvic examination however, ruled out the last possibility. The liver was not palpable and there were no tender areas. The urine and blood were normal.

Operation (Cullen): On opening the abdomen through a left rectus incision, the left kidney was found normal, the spleen was unaltered, and the mass lay behind the transverse colon and omentum. The omentum was opened up between the transverse colon and stomach and the mass was drawn out as far as possible, and was found to be cystic and multilocular. By puncture, 1000 cc. of a yellowish-tinged fluid with a shimmer over its surface was drained out, which revealed the presence of cholesterin crystals and large epithelial cells with brownish pigment. A greater part of the cyst was removed, leaving only a small cuplike depression 6 cm. deep. In removing the cyst a great portion was found multilocular in character, and in the walls of the large cyst were smaller ones, some 1.5 cm. in diameter, and there was a large cystic area 8 by 5 cm., which was composed of numerous smaller ones. The cyst wall was sutured to the anterior abdominal peritoneum and the cyst drained. The patient made a satisfactory recovery and was discharged, August 3, 1918.

At an examination on October 11, 1923, although the patient felt per-

fectly well, a cystic mass was detected just beneath the scar which had appreciably increased in size. On December 12, 1924, a large prominence was noted just above the umbilicus, rising directly up from the abdominal wall. There was no doubt of a great accumulation in the old pancreatic cyst. On December 26 the patient was seized with severe abdominal pain and was removed at once to the hospital and operated on.

The old scar was removed and a cavity was immediately entered (pancreatic cyst) which was irregular in form with trabeculæ running through it. It contained 3 liters of a turbid slightly sticky fluid with a moderate quantity of white stringy material. The cavity was cleansed and packed.

The patient was extremely weak following the operation and made a slow recovery, and was discharged on February 24, 1925. The wound was still draining but the discharge was rapidly diminishing. The sac was greatly decreased in size.

CASE V.—*Pancreatic cyst; drainage and partial removal of cyst wall; abscess beneath incision about two and a half years later; frequent similar abscesses thereafter; development of carcinoma in sinus tract; patient died of cancer nearly seven years following operation.*

G. W. B., married, female, aged fifty-eight years, consulted us November 4, 1918. She complained of indigestion and especially of eructations and distention following meals, and of a mass which she had recently observed in the left upper abdomen. This varied considerably in size; recently being somewhat smaller; it was not painful. She had lost 25 pounds in weight, but was still fairly well nourished and weighted 132 pounds. Her menstruation stopped four years ago. Her appetite had been good until recently. Her bowels were regular.

On physical examination there was evidence of loss of flesh; the pulse, temperature and respirations were normal. The blood pressure was 160/100. The heart and lungs presented no abnormalities. The abdomen was perfectly flat, presented a small amount of adipose tissue, and was moderately relaxed. In the left upper quadrant a tumor mass was noted, which was freely movable, projecting down beneath the costal margin. It was relatively smooth, extending well beyond the midline. It was about 12 cm. from side to side and about the size of a large cocoanut. It presented no sharp margin, and was not tender to pressure. The spleen was not palpable, and there were no other palpable masses.

The vaginal outlet was moderately relaxed; the cervix somewhat lacerated. The body of the uterus was prolapsed on the bowel, but was not enlarged.

The urine was normal with the exception of a few hyaline casts, which it contained upon a number of examinations. The Wassermann blood test, negative; hemoglobin, 65 per cent; red blood cells, 3,900,000; leukocytes, 9500. The differential count was normal.

The gastric contents following an Ewald test breakfast revealed a total acidity of 30; free hydrochloric acid, 16. The stool was of medium size and contained a slight quantity of mucus; blood was not present.

A Roentgen ray examination presented a huge defect on the greater curvature of the stomach, produced by a mass from without.

The diagnosis of a possible splenic tumor was made, and the patient was admitted to the Church Home and Infirmary on December 18, 1918 and operated (Cullen) on the following day.

Even under deep anesthesia it was absolutely impossible to determine the exact nature of the mass. A left rectus incision was made, and beneath the fold of the transverse colon the tumor became clearly outlined. It was rather bluish in color and the peritoneum slipped over it very easily. The spleen was easily palpated and, apart from a few adhesions, it was

normal. The left kidney was unaltered. It at once became evident that we were dealing with a pancreatic cyst. The cyst was walled off, the peritoneum split, and a trocar introduced. The fluid was of a rather dull chocolate color, and opaque; as it flowed out, the cholesterin crystals were clearly in evidence, although they were not as distinct as we have noted at similar operations. However, the characteristic shimmer was distinctly recognized. The sac was gradually loosened, and about 1000 cc. of the fluid were removed. As much of the redundant wall as possible was cut

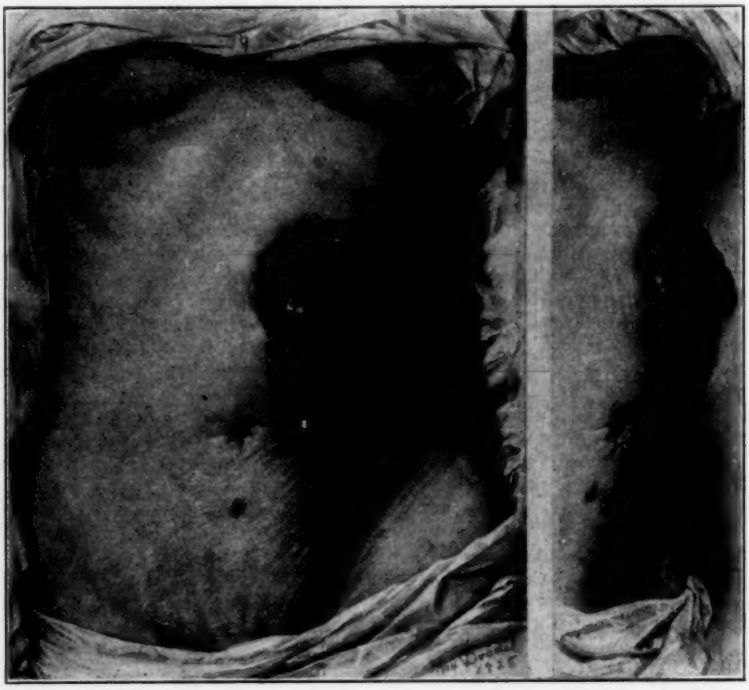

FIG. 1.—Adenocarcinoma developing in the sinus tract, several years after drainage of a pancreatic cyst. C. H. I., Nos. 20464 and 36386. J. H. H., Gyn. Path. No. 30276. Occupying the site of the former drainage tract is a large, friable growth that wells out in the center. It projects some distance from the abdominal wall, as indicated by the drawing to the right. Below the main growth is a small fistulous opening leading down to the cancerous tissue in the depth. For the histologic picture see Fig. 2.

away. We then whipped over the edge of the sac wall in order to check hemorrhage. The wall of the sac was then attached to the abdominal peritoneum at five or six points and lightly packed with cigarette drains between the sac wall and the peritoneum of the abdominal wall in the intervening spaces. The sac itself was filled with three or four pieces of 3-inch gauze.

The wall of the sac varied from 0.5 mm. to 2 mm. in thickness. The patient quickly recovered from the effects of the operation, had a satisfactory convalescence, and was discharged, January 29, 1919. When examined on April 10, 1919, the patient was found in good condition; the

abdominal scar was quite normal with the exception of a slight scale at a single area where there had been some stretching of the incision. There was no thickening of any moment at this point.

On July 11, 1921, the scar presented a halo of redness extending about 2 cm. around it. In the center of the scar a rupture was observed. To the left of the incision there was a doughylike sensation noted on palpation as if an abscess had formed.

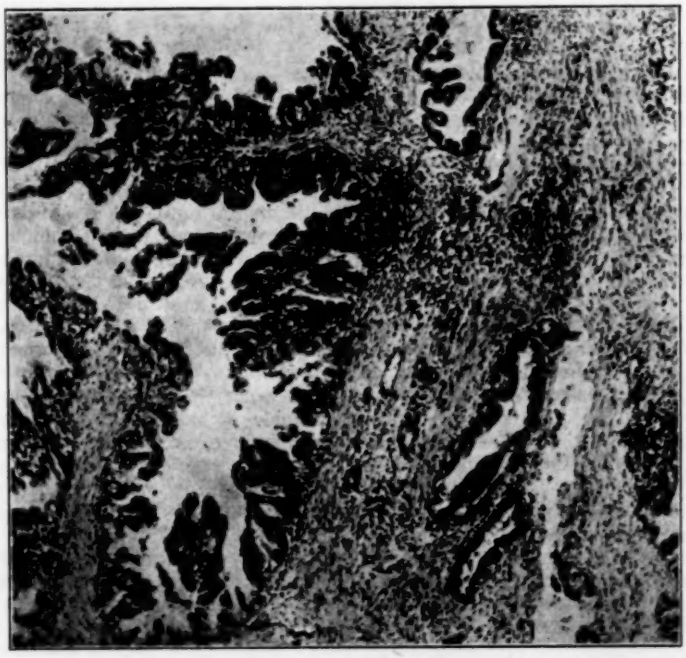

FIG. 2.—Adenocarcinoma developing in the fistulous tract, several years after drainage of a pancreatic cyst. C. H. I., Nos. 20464 and 36386. J. H. H., Gyn. Path. No. 30276. The superficial portion of the growth was necrotic. This section was from the tissue about 1 cm. beneath the surface. There is a definite papillary arrangement. Projecting into the larger gland cavities are many irregular finger-like processes made up entirely of epithelial cells. For the gross appearance see Fig. 1.

The patient failed to report for further examination until April 22, 1925. She was brought to the hospital in an extremely weakened condition, and presented a history of having been well for three years following the operation. Continuing on from this time she had had abscesses (about 30 in all) in the old scar. These were extremely tender and often continued on for many weeks. Following the application of poultices, relief was afforded after these had ruptured. She had lost much flesh and had had diarrhea at times, loss of appetite and a rise occasionally in temperature was also noted.

An examination at this time revealed a thin anemic individual who evidently had lost much flesh, and gave the appearance of being extremely ill. Her mucous membranes were pale, and she evinced signs of abdominal pain.

The left axillary glands were much enlarged though no enlargement was noted in any other glands. The heart was not enlarged, but there was a soft systolic murmur at the apex, the pulse was slightly irregular and weak.

The abdomen was soft, but in the left upper quadrant of the abdomen below the costal arch a mass was palpable about the size of a grape fruit, which was solid, hard, tender, not movable and not fluctuating. On examining along the line of the old incision an area was noted which seemed to be literally welling out of the abdominal cavity. This was several centimeters in diameter and projected about 1.5 cm. from the surface of the abdomen. In the outlying portion it was covered with skin, but in the center it had a reddish appearance. The skin was thinned out at this point, and in places had disappeared, the new growth standing out clearly. The entire central portion of the raised area reminded one of a crater partially filled with debris, discharging a profuse amount of necrotic foul-smelling tissue. A portion of the tissue was removed for examination. The patient rapidly lost ground, and died October 30, 1925.

Pathological Report. The superficial portion of the growth presented marked polymorphonuclear infiltration, fragmentation of nuclei and debris. Beneath this, there is a regular papillary growth consisting of connective tissue with multiple glands on its surface. There can be no doubt but that the growth is an adenocarcinoma.

CASE VI.—*Pancreatic cyst observed for two years; drained by Dr. G. L. Todd, of Princeton, W. Va.; second drainage of cyst eight years later; changes in cyst wall indicating malignancy; death six months following second operation.*

E. G. T., married, male, aged fifty-six years, first consulted us December 19, 1920. He had been affected with attacks of indigestion for the past twenty years. These attacks would appear suddenly with colicky pain and gas. The last attack appeared six weeks ago, and lasted two to three hours. Periods as long as a year would frequently intervene between attacks, and in the intervals the patient enjoyed good health. He had measles, mumps, scarlet fever and whooping cough in childhood. In 1900 he had typhoid fever and five years ago was operated on for a pancreatic cyst; he was in the hospital ten days, and the cyst drained. For two years previous to this operation the attacks of acute indigestion were extremely frequent and severe; there was however, at that time no evidence of the presence of any abdominal mass. There have been a number of attacks since operation, but these have been far less frequent than previous to this procedure. The patient's appetite has since been good, his bowels regular; he has been affected however with eructation and flatulency.

On physical examination he presented the appearance of a rather thin individual, weighing 132 pounds, but claimed that he had not varied 5 pounds in weight in ten years. The thoracic organs showed no abnormalities. The blood pressure was 135/80. The abdomen was soft and presented a right rectus scar about 6 cm. in length and another 8 cm. in length on the left side, showing evidence of a former drainage wound at its center. The liver and spleen were not palpable and there was no tenderness anywhere over the abdomen. Just to the left of the median line there was a rather smooth globular mass about 5 cm. in length and 5 cm. in breadth. It was somewhat movable, not tender, and was relatively smooth everywhere. It extended from the left rectus incision to the median line.

The urine was normal. The Wassermann blood test was negative. The hemoglobin was 80 per cent; red cells numbered 4,150,000; leukocytes, 5800. The gastric contents following an Ewald test breakfast revealed a total acidity of 28, free hydrochloric acid, 8. The stool was fairly large in size, solid and light in color, and contained no mucus or undigested food matter; blood was absent. The duodenal contents was turbid, yellow and

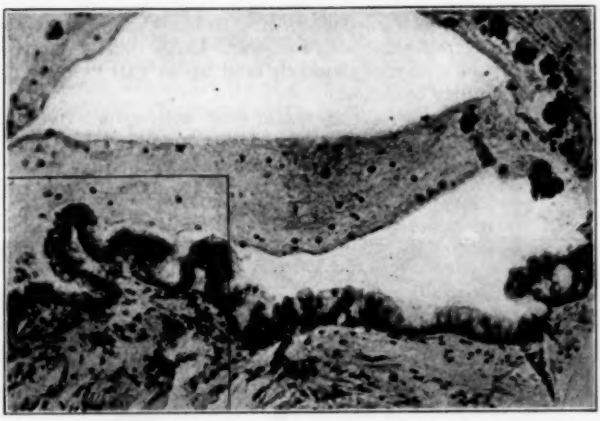

FIG. 3.—Epithelial lining of a pancreatic cyst (×100). C. H. I., No. 29817; C. H. I., Path. No. 3708. Small folds project into the cyst cavity. The epithelial lining is high cylindrical in type. For the high power of the small square in the left lower corner see Fig. 4, and for the high magnification of the dark clumps of cells in the right upper corner see Fig. 5.

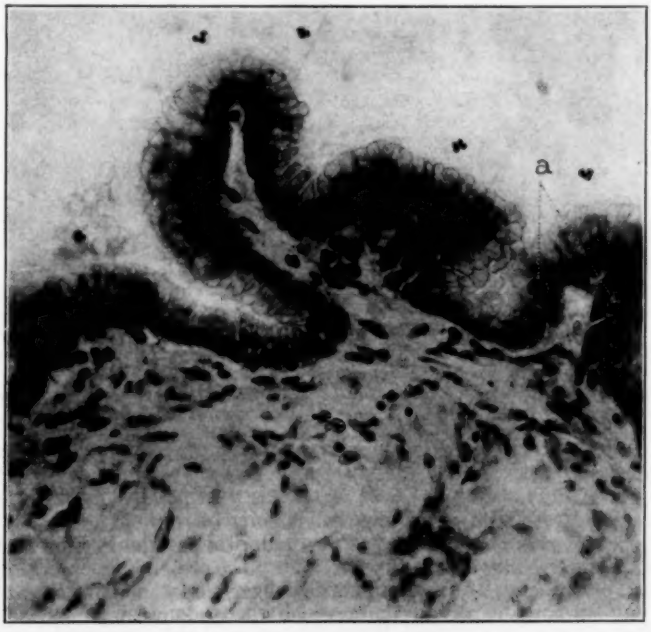

FIG. 4.—Epithelial lining of a pancreatic cyst (× 300). C. H. I., No. 29817; C. H. I., Path. No. 3708. This is enlarged from the square noted in Fig. 3. The epithelial cells are of a very high cylindrical type. There is evidently some cell activity, as noted by the two mitotic figures seen at *a*. (Retouched.)

contained mucus, cholesterin crystals and bilirubin with amylopsin 2; trypsin and steapsin 1, examined according to the Einhorn method.

The Roentgen ray report was as follows: Large defect in the stomach due to pressure from without; stomach held up in gall bladder region by adhesions; liver slightly enlarged.

The diagnosis was made of pancreatic cyst with upper right quadrant adhesions. The patient would not remain for operation and was not seen again until January 13, 1923. He then presented a history of having had occasional attacks of acute abdominal pain during which a large mass

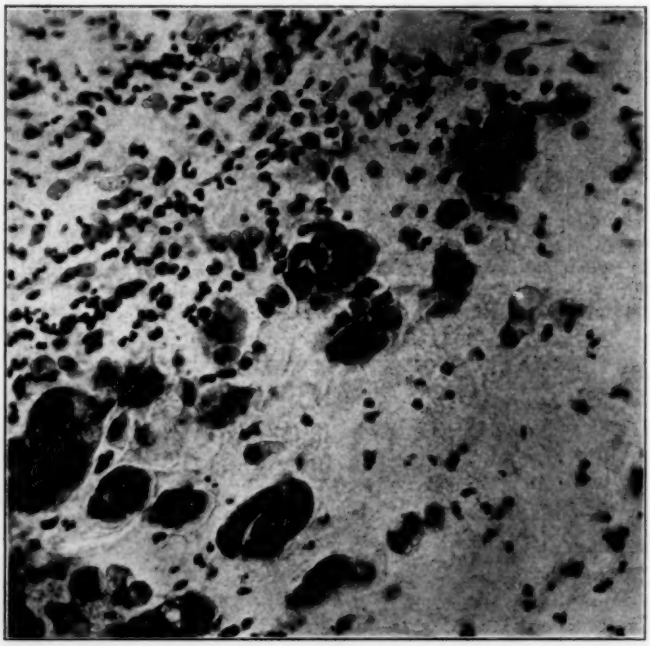

FIG. 5.—Suspicious epithelial cells, some lining the cyst wall, others scattered throughout the underlying stroma in a pancreatic cyst (× 300). C. H. I., No. 29817; C. H. I., Path. No. 3708. Some of these cells are unusually large and have large nuclei. In others the chromotin is very black. At numerous points are giant cells containing a varying number of dark nuclei. Nearly all of these cells are unusually well preserved. They do not in any way resemble foreign-body giant cells. Even more suspicious areas were noted in the stroma of the cyst wall. (Retouched.)

could be easily outlined in the upper abdomen which would almost entirely subside in the intervals; the patient was under the firm impression that the size of the mass changed from time to time. The present attack, which had its onset on January 2, 1923, had lasted longer, and had been more severe than any formerly experienced, in which the abdominal pain ordinarily subsided within a few hours. Since the onset of this attack his appetite had been poor, the bowels had been regular though slight relief of pain had been obtained by means of enemata. He had lost considerable flesh.

On physical examination the patient was found somewhat emaciated, his temperature was normal; pulse, 114; respiration, 20; heart and lungs

were normal, and the radials somewhat sclerosed. On inspection of the abdomen a decided fullness was observed in the epigastrium and also in the left hypochondrium especially in the axillary line. On palpation a large firm irregular mass was noted bulging out from under the left costal arch and occupying almost the entire epigastrium, hypochondrium and upper lumbar region. The lower margin extended about 1 cm. below the umbilicus. The mass was hard and firm in the epigastric area, while that portion occupying the left hypochondrium was soft and gave one the impression of a cyst formation. The liver and spleen were not palpable. The diagnosis of pancreatic cyst was made and operation decided on.

Operation (Cullen), January 16, 1923: A right rectus incision was made, but upon exploration the liver was found so adherent to the abdominal wall that it was decided to abandon this area of exposure in favor of a left-rectus incision. The omentum was split, the cyst opened, the walls of which varied from 3 to 4 mm. in thickness. Glairy-white, sticky material was encountered, deeper in the cyst flocculent material was seen, and in the cyst wall at one point a spicule of calcification was noted. The sac contained about 1000 cc. of fluid. One deep pocket passed down to the left, another to the right. On account of the adhesions no attempt was made to remove any portion of the sac. The sac was cleared out and the cavity filled with gauze and the sac wall was then stitched to the abdominal incision. The gall bladder was next separated from the anterior abdominal wall. The patient stood the operation well, and steadily improved. Until his discharge on March 30, 1923, the cavity drained a thick mucoid material which was in no way influenced by the introduction of alcohol and other fluids, which were utilized with the hope of securing superficial necrosis of the cyst cavity. The cyst however gradually decreased in size until it would no longer hold more than an ounce of the irrigating fluid. The patient gained in weight and his general health continued to improve; but after returning home he gradually lost weight and strength, developed jaundice and died in July of carcinoma of the liver (probably secondary).

An examination of the discharge obtained from the cyst revealed a glairy-white fluid filled with pus cells and fatty acid crystals, but containing no pancreatic ferments. Section of a bit of the cyst wall removed at operation showed it to be composed of fibrous tissue and lined in some area by a very high and somewhat undulating cylindrical epithelium. At other points were little regular or irregular glands lined by an altered epithelium and here and there the gland cells had increased markedly in size, and contained masses of the chromatin. This picture was most suspicious of adenocarcinoma.

CASE VII.—*Pancreatic cyst; partial excision and drainage; recovery.*

L. P., male infant, aged sixteen months, was admitted into the surgical ward of the Johns Hopkins Hospital on October 9, 1925, on the service of Dr. Dean Lewis to whom we wish to express our indebtedness for allowing us to report this case. The past history of this patient was unimportant. He had not been affected with any of the usual diseases of childhood.

At twelve months of age there had been an attack of diarrhea and since that time the abdomen had gradually enlarged, though the weight has not materially increased. A few days ago a mild attack of diarrhea and some vomiting recurred. There were two to five stools daily, whitish in color, with an offensive odor.

Physical Examination. The weight of the child was 22½ pounds. Temperature, 98.6; pulse, 112; respirations, 30. The heart and lungs were normal. The abdomen was large, and protruding; circumference of upper abdomen 21½ inches; in umbilical region 19 inches. It was soft with shifting dullness on change of position; succussion wave could also be

detected on tapping the abdomen. There was no evidence of abdominal tenderness or muscle spasm. A firm slightly irregular mass could be detected on the right side of the abdomen in the umbilical region. The liver and spleen were not palpable. The diagnosis of mesenteric cyst was made. Operation was performed by Dr. Dean Lewis on October 14, 1925. The abdomen was opened to the right of the median line in the lower half and a large cyst detected. A trocar was inserted and 750 cc. of a milk-like fluid was removed. When the cyst wall was drawn from the abdomen it was found to pass out from behind the stomach, through the transverse mesocolon; becoming most prominent in the gastrocolic omentum, and was adherent to the middle colic vessels on the left and to the under surface of the duodenum. Part of the wall was resected and a tube inserted which was closed off by a purse-string suture. The cystic mass was definitely pancreatic in nature.

After operation but a slight amount of blood-tinged drainage was noted. Cultures and smears of the fluid showed no organisms. The fluid contained no trypsin and but one unit of amylopsin. The drainage tube was removed on October 26, 1925, and the sinus was entirely closed in fifteen days following operation. The patient was discharged as well on November 3, 1925. There has been no further evidence of filling up of the cyst.

Etiology. The formation of pancreatic cysts has been carefully studied by Dieckhoff,[16] Tilger[17] and Lazarus.[18] Mayo Robson and Cammidge[2] classify pancreatic cysts as follows:

1. Retention cysts, which are lined with epithelium and are caused by obstruction in the pancreatic duct, smaller ducts or acini.
2. Proliferation cysts due to proliferation of glandular epithelium followed by an accumulation of fluid. These are true tumor formations (cyst adenomata or cystic epitheliomata).
3. Congenital cysts.
4. Hemorrhagic cysts due to hemorrhagic necrosis.
5. Hydatid cysts.
6. Pseudocysts produced by trauma or degenerative changes of the interstitial tissue of the pancreas. They are distinguished from true cysts in that they are not within the substance, of the pancreas but without it and usually in the lesser omental sac. They have no epithelial lining. Primrose[19] has correctly added a seventh type dermoid cysts.

Many conditions have been recorded as causative factors in the production of pancreatic cysts. Of these to be noted are acute and chronic pancreatitis, and especially chronic interstitial pancreatitis producing pressure on the ducts due to the contracting fibrous tissue and to cholecystitis. As interesting evidence in this direction, biliary colic with jaundice has been noted preceding the cyst formation. Constriction of the smaller ducts may lead to multiple sacculations and smaller cysts. Following obstruction of the ducts infection may occur with the further development of a true retention cyst.

Cases of this type have been reported by McPhedran,[20] Castronuova[21] and Ballin and Saltzstein.[22] In McPhedran's case a cyst

occurred following gall stone attacks and acute pancreatitis; in Castronuova's, following treatment of syphilis of the liver; in Ballin's and Saltzstein's, following acute pancreatitis after removal of the gall bladder for stones; in Case III of our series, three months following the operation for gall stones.

Proliferation cysts according to Oser[23] are rare and are to be looked upon as the production of cystic formation in tumors or as cystic degeneration of the pancreas similar to that occurring in the kidneys, testes or mammary gland. Cases of this type have been reported by E. Dieckhoff[24], Zukowski[25] and Garrigues.[26] Hemorrhagic cysts must be distinguished from retention cysts containing blood. In this type the hemorrhage in the primary condition which is followed by cyst formation. Hemorrhagic cysts, according to Oser, are single, larger and develop in the tail of the pancreas, and the contents are extremely hemorrhagic. Le Dentu,[27] Becourt[28] and Parson's[29] report cases of cystic formation of this type following trauma.

In a certain proportion of instances there is a direct history of trauma noted in the production of cysts of the pancreas. This is especially observed in the formation of the pseudocysts. The true pancreatic cyst wall consists of dense fibrous tissue which is ordinarily lined with cylindrical epithelium though in some instances the epithelial lining may disappear due to atrophy from pressure of the cyst contents and from circulatory or inflammatory disturbances in the cyst wall. The surface of the cyst is smooth and is ordinarily not adherent to neighboring organs. One or more ducts are usually noted in the cyst which in some instances communicate with one another.

Pseudocysts usually due to trauma, often to blows upon the abdomen, have a thick inflammatory capsule which is usually adherent to neighboring organs. They possess no epithelial lining and the wall consists of the peritoneal boundary of the sac and neighboring organs. Dermoid cysts of the pancreas have been noted by Judd[30] and Dennis.[31]

The attempt at experimental production of cysts has not always been followed with success. Senn[32] was unable to produce a cyst by sudden and complete obstruction of the pancreatic duct, although he noted slight dilatation of the duct beyond.

Thiroloix,[33] however, was able to accomplish this by ligating the duct and injecting a mixture of soot and carbolized liquid vaselin. Experiments in which crushing of the pancreas was performed have ordinarily failed in the production of cyst formation, though Lazarus[34] produced small cysts by this method in a single dog, a hematoma was first noted and a cyst containing 100 cc. of fluid followed in forty days.

A number of clinical observations have been recorded in which cyst formation has occurred following obstruction due to various

conditions such as pressure due to stone in the common duct. (Phulpin,[35] Engel,[36] Horrocks and Morton;[37] pancreatic duct Tricomi[38]), or parasites (Durante)[39] or tumor scar tissue (Cruveilhier,[40] Virchow,[41] Friedreich[42]).

Cysts vary greatly in size from that of a pigeon egg to such an extent as to fill a large part of the abdominal cavity, containing at times as much as 10 to 15 liters of fluid. Ordinarily the size according to Robson and Cammidge[2] is about that of a child's head. Cysts of large size have especially been noted associated with cholecystitis in which a stone was lodged near the orifice of the pancreatic duct. Cases of this type have been reported by Phulpin[35] and Horrocks and Morton.[37]

Cysts of the pancreas grow slowly and cause but slight evidence until sufficient pressure is produced on neighboring organs. At times however, they appear suddenly, and grow rapidly often due to sudden hemorrhage in the cyst itself as a result of rupture of the bloodvessels in the wall. On the other hand large cysts may disappear suddenly due to rupture into the peritoneal cavity frequently following trauma, occasionally rupture may be spontaneous into the intestines, producing a discharge of the fluid through the bowel, ordinarily with temporary disappearance of the abdominal mass. Rupture occasionally occurs into neighboring organs.

As has already been noted pancreatic cysts may follow trauma upon the abdomen as was observed in Case II of our series. The period at which the cyst is first noted after the injury may vary from a few weeks to several years. The shape of the cyst varies according to its origin. It is usually spherical but may present a beaded, rounded or oval appearance according to whether it originates from the pancreatic duct or from the smaller ducts within the gland. It usually consists of a single large sac but may be multiple.

Pancreatic cysts are usually observed in middle life though they occur at any age. Both sexes are equally affected. In Oser's[23] series of 121 cases, 60 occurred in males and 61 in females; 62 occurring between the ages of twenty and forty years. In McWhorter's 19 cases the average age was forty years. In our series of 7 cases there were 4 females and 3 males, the ages varying between sixteen months and fifty-eight years. Drennan reported the case of a boy, aged four years, in whom this condition was produced by injury and in whom recovery followed operation. Telling and Dobson[45] recorded an instance in an infant and we have included in our report the case of Dean Lewis', an infant sixteen months of age. In Judd's[30] report of 41 cases of pancreatic cysts observed at the Mayo Clinic the ages varied between twenty-one and sixty-eight years; 24 were females and 17 males. Cystic tumors of the pancreas occasionally undergo malignant degeneration. Hartman[46] has described such a transformation in the tail of the pancreas with

metastases in the liver; 3 of our cases had undergone similar changes (Cases I, V, VI). On the other hand cystic degeneration may take place both in benign and malignant tumors of the pancreas. Such cases have been recorded by Lockwood,[47] Marogna[48] and Speese.[49]

Contents of the Cysts. The contents of pancreatic cyst vary. They are ordinarily alkaline in reaction, with a specific gravity of 1010 to 1020. They may be perfectly clear, though usually blood is present, often having undergone marked changes to a dark chocolate color or coffee-ground appearance. When the fluid remains uncolored it is often viscid in appearance due to the mucin in its contents. It frequently contains one or more of the pancreatic ferments and it is possible that all three may be present; amylopsin is of but slight diagnostic value as it may be obtained from other fluids in the body; steapsin is of more importance, while trypsin, when present, renders the diagnosis certain; however, an absence of the ferments does not in any way indicate that a cyst is not of pancreatic origin, for the ferments frequently disappear in old cysts (Opie[50]), often reappearing in the discharge when the cyst is drained. In addition the cyst contents contains epithelial cells, cholesterin, fatty globules and crystals, red blood cells and leukocytes and traces of mineral salts. The contents of the pseudocysts is a fluid produced by the liquefaction of necrotic tissue together with a bloody and inflammatory exudate.

According to Körte[3] the various locations occupied by pancreatic cysts may be grouped as follows:

1. Cysts developing in the lesser peritoneal cavity between the stomach and transverse colon, forcing the stomach up and the colon down.

2. Cysts developing from the upper border of the pancreas lying above the stomach, forcing in front the gastrohepatic ligament and producing a passage between the stomach and liver. This condition occurs less frequently inasmuch as but 12 cases of this variety having been recorded according to Körte.

3. Cysts occurring between the layers of the mesocolon; the transverse colon lying either in front of the cyst or above it.

Symptoms. The symptoms are not distinctive at first. There is present usually a prolonged history of indigestion and abdominal discomfort with pain of a colicky type not unlike that observed in mild forms of cholelithiasis. Occasionally however, pain is absent. Ordinarily as the cyst enlarges pain becomes more pronounced, due to stretching of the cyst wall and pressure upon other organs. This frequently occurs at intervals and may then be associated with nausea and vomiting. At times the symptoms may be so marked as to simulate those of intestinal obstruction. The pain is usually noted in the epigastrium and may be referred to the back or it may occur in the right or left hypochondrium according to whether the cyst is situated in the head or tail of the pancreas. In addition to

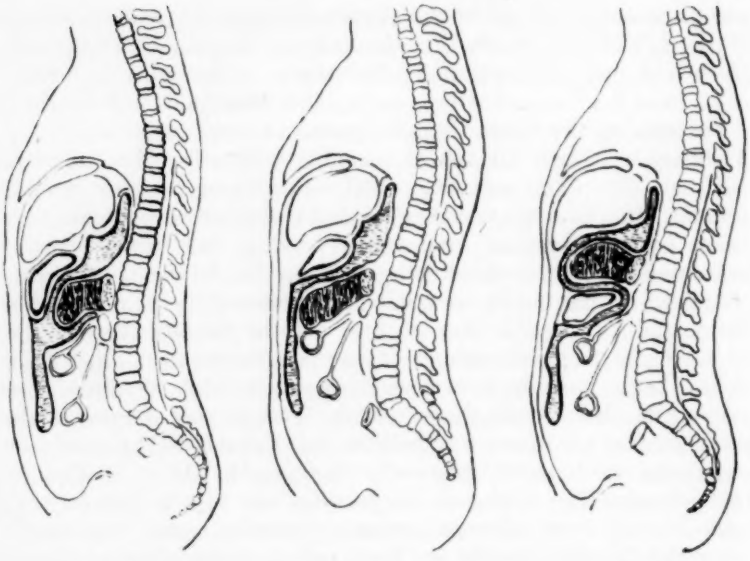

FIG. 6 FIG. 7 FIG. 8

FIG. 6.—Tumor of pancreas. Stomach in front, colon below.

FIG. 7.—Tumor of pancreas pushing forward between the posterior layer of the great omentum and the transverse mesocolon.

FIG. 8.—Tumor of pancreas. Stomach and colon both below.

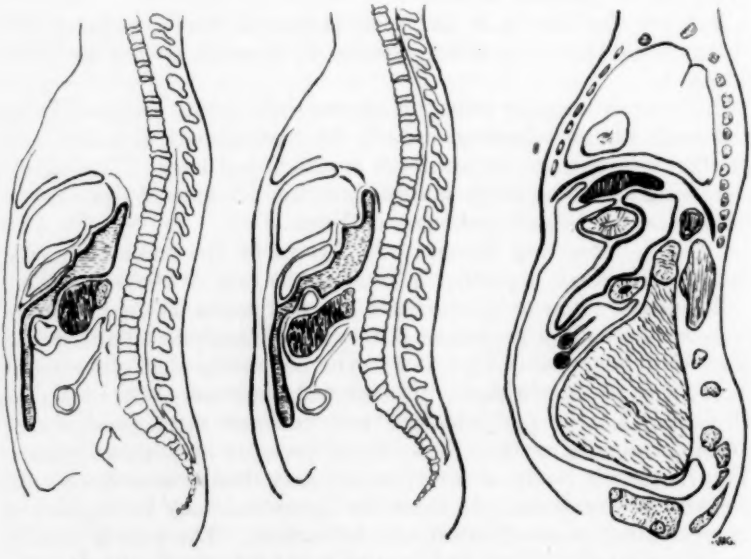

FIG. 9 FIG. 10 FIG. 11

FIG. 9.—Tumor of pancreas. Stomach and colon in front of it.

FIG. 10.—Tumor of pancreas. Stomach and colon both above it.

FIG. 11.—Tumor, cyst of pancreas. Stomach, colon and small intestine above and in front of it.

(Figs. 6, 7, 8, 9, and 10 from Robson and Moynihan. Fig. 11 from Primrose, *Pancreatic Cysts and Pseudocysts.*)

the pain or discomfort following meals, loss of appetite, gaseous distention and constipation are usually present. With the progress of the disease, there is progressive loss of flesh and weakness and because of pressure on other structures jaundice ascites and edema of the extremities, and even obstruction of the right ureter have been noted, and not infrequently abdominal distention and dyspnea. Diabetes and glycosuria have been observed in those instances in which the pancreatic duct has become obstructed with subsequent involvement of the islands of Langerhans. Rarely an increased secretion of saliva has been observed.

The most distinctive sign however, of the existence of a pancreatic cyst is the progressive enlargement of the abdomen with tumor formation situated between the xiphoid cartilage and the umbilicus. The mass produces a protrusion in the median line, but most frequently in the left hypochondrium and presents a distinct respiratory mobility; though the position of the cyst is but slightly altered by change in position except when its origin is in the tail of the pancreas. The surface of the cyst is smooth and although fluctuation is ordinarily noted, this sign may be absent due to the extreme tension producing the appearance of a solid mass. A cyst lying in front of the aorta may transmit the pulsation but this condition disappears when the patient assumes the knee-chest posture.

The sudden enlargement of a cyst with the appearance of shock and intense pain may be produced by hemorrhage from within and the sudden diminution in size with profuse diarrhea may be due to the evacuation of the cyst contents into the bowel. A disappearance of a cyst with signs of shock may indicate rupture into the peritoneal cavity. If the interstitial pancreatitis associated with cyst formation is extensive, there may be at times much loss of flesh, large fatty stools and sugar in the urine. Judd[30] has pointed out the frequent association of gall-bladder disease with this affection. He observed it in 17 instances of his 41 cases; diabetes was present in 3 cases. The location of the cyst can be frequently more easily determined by inflation of the stomach and colon; a small cyst may be entirely covered over by the stomach, but as it enlarges in size the stomach is ordinarily pushed up and the colon down.

Diagnosis. The diagnosis of cyst of the pancreas depends upon the physical signs together with the symptoms already noted. As a rule these cysts grow slowly and rarely become evident until they have attained a size sufficient to produce pressure upon other organs. In about a fourth of the cases, according to Korte,[3] they follow injury of the upper abdomen. However, between the time of the trauma and the time of the first detection of the cyst there may exist a period of a few weeks or even several years. In those instances in which the cyst is not due to injury there is usually a

period in which inflammatory and gastric disturbance with colicky pain precede the appearance of the cyst. A pancreatic cyst may be suspected when a fluctuating mass manifests itself in the epigastric area, and especially when situated to the left of the median line.

Considerable evidence as to the nature of the cyst is obtained as has already been stated by inflation of the stomach and colon. When the cyst is located as is usually the case between the stomach and transverse colon, on inflation, these organs will be observed on the opposite sides of the cyst. When the cyst occupies a position above the stomach on inflation it is crowded between the stomach and liver and the stomach and transverse colon come closely in contact with each other. In those instances in which the cyst has developed between the layers of the mesocolon the colon when distended either rotates upon the cyst or is situated somewhat above it.

In diagnosis attention must be called to the fact that when the cyst occupies the head of the pancreas the common duct is usually compressed, producing jaundice. When extensive involvement of the pancreatic tissue occurs with cystic formation large fatty stools may be observed with sugar in the urine.

The examination of the duodenal contents offers us but slight direct information as to the presence of pancreatic cyst, though Einhorn[51] noted a diminution of steapsin and trypsin in his cases.

The Roentgen ray may be helpful in diagnosis in ruling out the stomach, intestines and liver; though at times a large defect in the stomach or bowel may be produced from pressure of a cyst from behind, and thus lead to an error in diagnosis.

Differential Diagnosis. Pancreatic cysts may occupy any part of the abdominal cavity, and on this account alone the differential diagnosis may present many difficulties. The following conditions must be taken into consideration:

1. Echinococcus cysts of the liver: This form of cyst may produce a large fluctuating tumor in the epigastrium and considerable difficulty may be encountered in the differential diagnosis.

2. Omental or mesenteric cysts: These cysts are usually observed in the neighborhood of the umbilicus and are ordinarily accompanied by peritoneal irritation and ascites.

3. Distended gall bladder: The distended gall bladder has the respiratory motility of the liver and is not covered by the stomach or intestine, and the enlargement merges directly with that of the liver.

4. Ovarian cysts: Ovarian cysts can usually be easily detected by means of rectal and vaginal examinations.

5. Hydronephrosis: The mass produced by a hydronephrotic kidney fills the lumbar region and is forced further back by distention of the colon. Variations in size usually occur. The diagnosis

can be definitely established by means of urinary and cystoscopic examinations; the mass disappearing by catheterization of the ureter.

6. Aortic aneurysm: When a pancreatic cyst is intensely distended with fluid, pulsation may be transmitted from the abdominal aorta, thus simulating aneurysm. A knee-chest examination, however, will clear up the diagnosis.

Complications. The serious complications which may arise during the course of the growth of pancreatic cysts are:

1. Serious hemorrhage into the interior of the cyst due to rupture of large vessels in its wall.

2. Perforation of the cyst which may occur into the peritoneal cavity due to trauma or occasionally there may be a spontaneous rupture into the intestine.

3. Prolonged and extensive pancreatic disease, associated with the cystic growth, leading to marked loss of flesh and occasionally to diabetes.

4. Transition of a simple cyst into a malignant growth.

Course and Prognosis. The course of the disease is ordinarily slow though progressive, and serious manifestations may be occasioned, due to pressure on various organs or interference with the digestion, pancreatic involvement, as well as from rupture of the cyst. The prognosis depends largely upon the type of cyst and the operative procedure undertaken. Adenocystic tumors are ordinarily benign, grow slowly, but are difficult to remove inasmuch as they require partial extirpation of the pancreas, while simple drainage is apt to be followed by a permanent secreting fistula. Hamilton[52] was able to overcome this complication in his case by the use of radium.

Pseudocysts yield effectively to drainage. Patients with slowly growing cysts as a rule recover following operation while on the other hand the prognosis in acute cases with toxemia is extremely grave.

Treatment. Operation is always indicated. The procedures recommended are puncture, extirpation and drainage. Of these, puncture should always be avoided, both as a diagnostic as well as a therapeutic procedure, for should pancreatic fluid trickle into the peritoneal cavity, serious peritonitis would ensue. Complete extirpation of the cyst is dangerous and difficult as it frequently necessitates a removal of considerable of the pancreatic tissue. The operation has however, been performed in a number of instances successfully (Bozeman,[4] Willis and Budd[7] and others). Usually however, adhesions are so dense that removal is impossible. When the cyst occupies the tail of the pancreas or has a small pedicle complete removal is feasible. A complete extirpation as a rule will prevent the formation of a pancreatic fistula. Zweifel[5] removed a cyst with the entire pancreas with the exception of a small portion of the head; glycosuria ensued but disappeared within two months.

The operation most frequently performed and the one which has usually given most satisfactory results is isolating the cyst wall from the peritoneal cavity and draining following suturing of the cyst wall to the anterior parietal peritoneum. As much of the cyst wall as is possible should be excised. If the suture is entirely satisfactory the cyst may be incised at once and thoroughly sponged with gauze and finally drained through a rubber tube sewn into the opening and the abdominal wall closed around it. This procedure is known as marsupialization. However, if the suturing is not satisfactory the wound must be tamponed with gauze and the incision into the cyst postponed until adhesions have formed. Ordinarily the large cavity collapses and healing proceeds slowly and the secretion of pancreatic fluid may continue on in amounts from 500 to 800 cc. a day. Pancreatic ferments may be noted in the drainage from the wound following operation or may appear weeks later. Under favorable conditions granulations spring from the walls of the cavity and occasionally the inner lining of the cavity sloughs out. If the discharge comes in contact with the skin, it may produce a corrosive effect around the wound.

The disadvantage of the incision with drainage is the possible occurrence of a permanent fistula, hernia or occasional recurrence of the cyst. However, inasmuch as this operation can be performed with but little risk, it is to be recommended in most instances. Körte[3] notes that in a series of 141 drainage cases 7 patients died immediately following operation and 1 at a later date from infection. Of 22 cases of extirpation of pancreatic cysts there were 4 deaths, in 1 however, a fatal peritonitis existed at the time of the operation. Mayo Robson and P. T. Cammidge[2] collected 160 cases in which drainage had been performed, there were 140 recoveries; death followed operation in 20 and in 8 others death occurred later as the result of diabetes and other complications. In another series of 138 cases treated by incision and drainage death occurred in 16 cases. Of 15 cases with complete excision death occurred in 3.

Of 134 cases collected by Oser[23] there were 101 operations with 81 recoveries; incision with drainage was performed in 58 with 7 deaths; puncture in 7 with 5 deaths; extirpation in 11 with 2 deaths.

In the series of 41 reported by Judd no deaths occurred in 31 in which drainage had been performed. Extirpation was performed in 5 of the 41 cases.

Conclusions. 1. Pancreatic cysts are relatively infrequent, but yet occur sufficiently often to at times complicate the diagnosis of upper abdominal lesions.

2. The diagnosis is frequently difficult and cannot always be definitely established without surgical exploration. The main symptom pointing to this condition is the presence of a tumor usually noted in the left upper abdomen, the surface of which

is smooth. Fluctuation is at times observed. As a rule the mass can easily be differentiated from enlargements associated with the spleen, liver and left kidney. Not infrequently a filling defect is produced in the stomach, recognized by Roentgen ray examination which lends additional evidence of the presence of this affection.

3. The only proper treatment is early operation. The procedures to be undertaken are extirpation of the cyst if possible or drainage following suturing of the cyst to the abdominal wall, which is ordinarily more easily and safely accomplished. The results of operation are usually satisfactory.

4. A malignant degeneration of the cyst is, according to our experience, not an unusual complication; it occurred in 3 of our 7 cases.

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THE PREPARATION AND CLINICAL APPLICATION OF SCARLET FEVER ANTITOXIN.*

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Although scarlet fever antitoxin has had intensive clinical use during the past twelve months, there has been but little published during that time describing the experiences encountered in the preparation of scarlet fever antitoxin, and the clinical application of the antitoxin so prepared. We have, therefore, thought that it would be of interest and perhaps of value to many if we would report our results in these two particulars.

The results embrace in part the immunization of 84 horses, the concentration of the plasma obtained from these horses, and the clinical use of the refined globulin so obtained for passive immunization and therapeutic use. We have used in our work at various times five different strains of scarlet fever streptococci, and have followed quite closely the methods described by Drs. George F. and Gladys H. Dick in their publications on the production of toxin, and its use in the immunization of horses for the production of antitoxin.

We have tried various modifications for the production of scarlet fever toxin for the immunization of horses; but have finally adopted, almost as a routine procedure, the use of horse-meat broth containing 1 per cent peptone, 0.5 per cent sodium chlorid and 1 per cent citrated horse blood. The meat broth, with the peptone and sodium chlorid, is made with a final pH value of 7.5 to 7.8 after being auto-

* Read before the joint session of the American Association of Pathologists and Bacteriologists and the American Association of Immunologists, Albany, N. Y., April 2, 1926.

claved. The citrated blood in the proportion of 1 per cent is added immediately before inoculation with the seed culture.

Eight hundred cubic centimeters of the meat broth is put into 2000-cc. Erlenmeyer flasks and the inoculated broth is incubated for five days, at the end of which time 0.5 per cent phenol is added. The mixture is allowed to stand for twenty-four hours or longer, after which time it is either filtered through a Berkefeld filter, or is passed through a Sharples centrifuge. After sterility tests have been made to insure the sterility of the toxin, it is then tested by the procedure described by the Dicks[1] for the number of skin-test doses contained in each cubic centimeter.

The toxin made by us has varied from 20,000 to more than 100,000 skin-test doses per cubic centimeter. For the past several months, the horses being immunized have received at least one injection a week of the toxin testing 100,000 skin-test doses or more.

We have used human beings entirely for the testing of our toxin until recently, when we have begun the use of goats (as suggested by Dr. Kirkbride of the State Laboratory of Hygiene, Albany, N. Y.) for at least the preliminary tests. In all cases, the strength of the toxin made by us have been compared with the reaction obtained with the standard toxin distributed by the Hygienic Laboratory.

The scarlet fever toxin prepared by us for the Dick Test and for active immunization has been made from beef extract, and without the use of any alien serum.

Immunization of Horses. Our horses have been immunized by repeated injections, either of filtered scarlet fever toxin or of the cultures which have been passed through a Sharples centrifuge, using essentially the same technique as is employed in the immunization of horses for the production of diphtheria or tetanus antitoxin. Horses, in many instances, will stand large doses of strong toxin without any apparent reaction.

It is our usual custom to begin with an initial dose of 50 cc. of toxin containing at least 20,000 skin-test doses per cubic centimeter, and to double the dose at each subsequent injection until the animal shows some reaction, or until the volume usually employed by us has been reached.

In the beginning, horses are injected three times a week; but after the maximum volume of the injection has been reached, the injections are continued twice weekly. A few of the horses, in the beginning of our work, were given intravenous injections of live cultures, together with subcutaneous injections of filtered toxin; but it was our experience that such animals after a time showed the effects of this intensive treatment, and it was discontinued as a routine.

We now have under observation several groups of horses which are being treated with different methods of immunization in order to determine whether any particular method offers advantages over

others. It is our impression at this time, however, that the administration of the filtered toxin, or cultures passed through a Sharples centrifuge, all in all, has advantages over any other method for the production of scarlet fever antitoxin in that horses reach production in a shorter period of time, their general condition remains better, and the antitoxin from a group of horses averages high. We have never used the Dochez method of immunization as, in our opinion, the presence of open abscesses, with the danger of contamination by other bacteria, makes the method objectionable.

After the horses have been under treatment for about 90 days, a trial bleeding is taken from each animal and the serum is tested for its neutralizing properties against the standard toxin. At the same time, a pooled sample of these trial bleedings is tested. We have experienced considerable difficulty in obtaining satisfactory results with the test on the trial bleedings, due to the large number of individuals who were sensitive to the native horse serum. As a consequence, we have relied more upon the results obtained with the pooled sample than we have on individual trial bleedings. Several groups of horses, consisting of 12 to 17, have given us average plasma testing, within three months after the beginning of immunization, 5000 or more neutralizing skin-test doses per cubic centimeter. If the general condition of the horse remains good, there is a gradual increase in the potency of the plasma under continued treatment, although we are unable to say at this time how far this increase continues.

Preparation of the Antitoxin. Horses are bled not less than seven days after the last injection of toxin, and the plasma, after removal from the corpuscles, is preserved with 0.5 per cent phenol. From 200 to 300 liters of plasma are used for a single concentration. A sample of the mixed plasma, passed through a Berkefeld filter, is always kept from each lot, and tests are made on this sample at the same time that potency tests are made on the finished globulin. The plasma is concentrated by a modification of the Banzhaf method—using the same methods that are used for the concentration of diphtheria and tetanus antitoxin.

The average concentration of the last 2000 liters of plasma has given an antibody concentration of from 4 to 5½ times. The finished globulin has tested from 20,000 to 30,000 neutralizing skin-test doses per cubic centimeter, and we have never succeeded in obtaining antitoxin, even from selected horses, testing higher than the latter figure. In this particular, our experience is in accord with that of the Dicks who have informed us in a personal communication that they have "tested various samples from various sources and none tested even close to 50,000 neutralizing skin-test doses per cubic centimeter."

All of the scarlet fever antitoxin prepared by us has been standardized on children and not on adults, and this may probably

explain the failure by us to obtain antitoxin testing as high as that claimed to be made by some. The Scarlet Fever Committee Inc., which has tested each one of our lots of antitoxin, also use children exclusively for this purpose. From a comparison of the results obtained by us in testing our antitoxin on adults and on children, we are satisfied that results varying very widely will be obtained with the same antitoxin tested on the two classes of persons. It has been our routine practice to test each lot of antitoxin in a dilution of 15,000, 20,000 and 25,000 neutralizing skin-test doses per cubic centimeter, and these dilutions give us, as a rule, when children are used, results not difficult of interpretation. The antitoxin has been tested by us according to the method described by the Dicks[2] and which is as follows:

Method.—Standard streptococcus scarlet fever toxin supplied by the Hygienic Laboratory is diluted with sterile physiologic salt solution to contain ten skin-test doses in each 0.1 cc. The antitoxin is diluted to 100 times the strength to be tested. That is, if the tests are for 20,000 a dilution of 1 in 200 is made, and equal parts of the diluted toxin and the diluted antitoxin are mixed and incubated at 37° C. for one to two hours. One-tenth of a cubic centimeter of this mixture is injected intracutaneously into the upper third of the forearm of susceptible children. Control tests are made in each child consisting of the diluted toxin containing one skin-test dose and a serum control. Tests are read after an interval of twenty-four and forty-eight hours, and all tests showing a positive reaction with the serum control are eliminated from the final reading. A reading at forty-eight hours is important as many antitoxin dilutions will hold the toxin in combination for twenty-four hours, but not for forty-eight hours. Any reaction 1 cm. or more in any diameter of the toxin-antitoxin mixture injection is considered a positive reaction and evidence of failure of neutralization of the toxin by the antitoxin.

Clinical Application. The suggestion has been advanced that scarlet fever antitoxin prepared in one locality was not specific against scarlet fever in widely separated sections of the country, and it, therefore, seemed to us important to obtain results on the use of scarlet fever antitoxin, prepared in a single laboratory, in widely separated sections.

We have been furnished by the directors of three hospitals with results from the use of scarlet fever antitoxin prepared by us—these hospitals being located in Illinois, New Jersey and Pennsylvania. We believe that the results about to be reported definitely establish the specificity of scarlet fever antitoxin so prepared for the various types of scarlet fever occurring in different sections of the United States. In addition to the cases here reported, we have also received reports on the use of this antitoxin in Detroit, Boston, Minneapolis, Kansas City, Pittsburgh, San Francisco, North Carolina and other

places, and the reports are all to the same effect. Any one who has had experience with the use of scarlet fever antitoxin cannot fail to be impressed by the quick response when adequate doses of antitoxin are given in the early stages of scarlet fever. The intravenous administration in such cases of adequate doses of properly prepared and standardized scarlet fever antitoxin is followed by a fall of the temperature to normal with twenty-four hours, a marked diminution of the rash, improvement in the general condition of the patient, and particularly a reduction in complications and sequelæ. The results from the intramuscular injection, while equally striking, are not as prompt.

Antitoxin for Passive Immunity. There have been not a few reports of the failure of antitoxin, when given as a prophylactic, to prevent the development of scarlet fever within two weeks after administration; but examination of these cases reveals the very interesting fact that failure to protect was due to inadequate amounts of antitoxin. The Doctors Dick have advanced the idea that most susceptibles who have been exposed to scarlet fever are either in the late incubation period or the early stages of the disease when the prophylactic dose of antitoxin is administered, and that therefore what these patients need is not a small dose of antitoxin, but a therapeutic dose. They, therefore, advise that not less than half the therapeutic dose be used as a prophylactic dose. Most of the cases reported by us were given half of the therapeutic dose of that particular lot of antitoxin—the dose administered varying between 75,000 and 150,000 neutralizing skin-test doses per cubic centimeter. We have reports on the use of the antitoxin on 184 contacts with scarlet fever, in each of whom there had been direct exposure to the disease. The Dick test made seventy-two hours after administration of the antitoxin was negative in each instance.

Not one of the 184 developed scarlet fever. We are satisfied from the results of the cases reported to us that the prophylactic dose of antitoxin should be at least one-half of the therapeutic dose.

Therapeutic Use. We have a record of 130 severe and moderately severe scarlet fever cases in three institutions in three different states treated with antitoxin, together with 84 cases in these same institutions who received no antitoxin. It is to be noted that the mild cases were not given antitoxin, while the severe and moderately severe cases were given antitoxin, and therefore the antitoxin was submitted to the severer test. Among the 130 cases, some of which were very severe cases with marked toxemia, there were no deaths, and there were only 4.6 per cent with complications—none of which were of a severe character or requiring surgical intervention. Of the 84 mild cases without antitoxin, there were no deaths, but 28.6 per cent had complications and sequelæ of varying degrees of severity. Some of the complications were of a grave character, requiring surgical intervention, and others entailing a long period

of convalescence. The complications in the untreated cases consisted of nephritis of a serious grade, otitis media, mastoiditis and suppurating cervical adenitis. The amount of antitoxin as given in the three hospitals is shown in the following table:

DOSAGE. EXPRESSED IN THE NUMBER OF NEUTRALIZING DOSES.

Hospital.	Maximum.	Minimum.	Average.
A	520,000	80,000	221,750
B	300,000	75,000	137,850
C	600,000	200,000	256,800
Average for all cases			184,000

It is to be borne in mind that all of the antitoxin used in the 130 cases referred to in the above table was unusually accurately standardized. The results in every instance have been determined by at least two independent observers—one in Chicago and one in New Brunswick—and in some instances by three different observers. In view of these results, obtained with the use of carefully standardized antitoxin, we are inclined to believe, for the present, that a therapeutic dose of antitoxin having at least 200,000 neutralizing skin-test doses is effective in the average case of scarlet fever, and may, therefore, be considered as the average dose. Of course it is recognized that severe cases, or cases seen late, may require larger or repeated doses.

We quote below a statement from the director of one of the hospitals where a large number of the cases here reported were observed and which sums up, in our opinion, the present status of the treatment of scarlet fever with antitoxin.

"By comparing the serum-treated cases with those not receiving the serum treatment, we have found the following results: By use of antitoxin we are able to obtain a more rapid subsidence of toxemia, more rapidly fading rash, more prompt return to normal of the mucus membrane, and a reduction in the number and severity of complications. The patients look and feel better, and are more comfortable."

Summary. Specific scarlet-fever antitoxin may be prepared by the immunization of horses with filtered toxin.

Such antitoxin is specific against scarlet fever occurring in widely separated sections of the United States.

A properly prepared and standardized antitoxin is effective as a prophylactic when used in adequate doses.

When used for passive immunization, it should be given in not less than one-half of the average therapeutic dose.

A properly prepared and standardized scarlet-fever antitoxin is effective in the treatment of scarlet fever, saving life and reducing the severity and frequency of complications.

REFERENCES.

1. Dick and Dick: J. Am. Med. Assn., 1925, **84**, 1477. 2. Ibid., 803.

THE PRESENT STATUS OF MERCUROCHROME-220 SOLUBLE.*

By Herbert H. Davis, M.D.,
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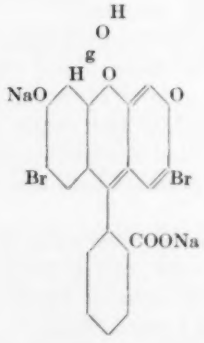
There have been so many conflicting reports written about mercurochrome that one is at a loss to know when to use it. In an attempt to get at this question, I am reviewing the literature as far as experimental work is concerned. The case reports in the literature are so biased and lacking in controls that they are very likely to throw one into error. Because of this I am not considering them in this discussion. Also, I am summarizing a little experimental work which I have done at the Department of Experimental Surgery at the University of Nebraska Medical College. My conclusions are in no way final and are subject to change as more work is done on the subject.

Mercurochrome-220 soluble was developed in 1919, by Young, White and Swartz in the Department of Urology at Johns Hopkins. The properties that were sought, and which were quite well shown by mercurochrome-220 are: (1) Ready penetration of tissue; (2) lack of irritation to tissues; (3) high germicidal activity; (4) ready solubility in water and stability of solution; (5) a drug not precipitated by urine; (6) low toxicity.

Mercurochrome-220 is the sodium salt of dibromoxymercuryfluorescin which contains 26 per cent of mercury. The structural formula is:



The free acid of dibromoxymercuryfluorescin is insoluble in water, but readily soluble in sodium hydroxid causing a deep cherry-red color and showing fluorescence on dilution. The sodium salt, however, is soluble in water.

Favorable Evidence. Young, White, and Swartz[11] catheterized a rabbit and injected 1 ounce of 2 per cent mercurochrome into the bladder. The animal was killed five minutes later and necropsy

* Read before Omaha Clinical Club, March 16, 1926.

showed the epithelial cells of the urethra reddened, especially superficially. The submucosa was also stained in places and the dye even penetrated into the muscularis. The glands of the urethra were stained for some distance from the mouths of the ducts. In regard to the toxicity they found that 10 mg. per kilogram of body weight intravenously invariably killed; a rabbit receiving 5 mg. per kilogram, showed decrease in phenolsulphonephthalein output of the kidneys and also a transient albuminuria lasting sometimes as long as a week. Dogs tolerated the drug better. Ten milligrams per kilogram were stood without discomfort, but there was produced a transient albuminuria and temporary reduction of phenolsulphonephthalein output, but no rise of blood urea, or evidence of permanent damage. They claim the drug is effective in both acid and alkaline urine but slightly more so in acid urine. In one minute it kills Bacillus coli or Staphylococcus aureus at a dilution of 1 to 1000. In fifteen minutes its effect is nearly as great as at twenty-four hours, killing Bacillus coli at 1 to 5000 and staphylococcus as 1 to 10,000. In 1 to 100 dilution it kills staphylococcus in ten seconds or Bacillus coli in thirty seconds.

Hill and Colston,[26] after injecting it intravenously, tested the bacteriostatic action of mercurochrome in the urine. Their method was to collect urine and to add one loopful of a twenty-four hour culture of Bacillus coli to 2 cc. of this urine. With intravenous injection varying from 1 to 10 mg. per kilogram they found the urine bacteriostatic and the greatest inhibiting power one to two hours after intravenous injection.

Hill and Colston[27] also tested the bacteriostatic action of mercurochrome on the blood of rabbits. The doses of mercurochrome used were 1, 2.5, 5, and 7.5 mg. per kilogram of body weight. Specimens of blood were removed just before injecting and also fifteen, thirty, forty-five and sixty minutes after injection. They were mixed with sterile sodium citrate to prevent clotting and 2 cc. of the blood was inoculated with one loop of a twenty-four hour beef-infusion broth culture of Bacillus coli. In thirty seconds 0.1 cc. of this blood culture mixture was removed, diluted, and plated. It was found that the greatest bacteriostatic action was from fifteen to forty-five minutes after injection. From this time on the action rapidly disappears.

To test the effect of intravenous injection on the kidneys, Hill and Bidgood[28] injected rabbits with varying doses between 1 and 10 mg. per kilogram of body weight. They killed these rabbits two days after injection, and there were no gross changes found; but microscopically in those receiving 5 mg. or over per kilogram there was slight congestion and cloudy swelling of the kidneys. Therefore, they concluded that any dose over 5 mg. per kilogram was dangerous. A second series of experiments was performed on rabbits to see if there was added damage to kidneys by repeated

injections. In Group A, after 12 doses of 1 mg. per kilogram, two injections per week, necropsy showed normal kidneys. In Group B, after 12 doses of 2.5 mg. per kilogram, two injections per week, necropsy showed kidneys normal except for slight congestion and cloudy swelling. In Group C, after 12 doses of 5 mg. per kilogram, two injections per week, necropsy showed slight congestion of the glomeruli, also mild dilatation and slight swelling of the tubules but no epithelial destruction. The lumina were partially occluded by edema of the epithelium and in some there was an exudate. They concluded that repeated doses caused no more damage than one injection. Another group of rabbits was given repeated injections but the animals were not killed until two months after the last injection. These showed no renal damage.

Piper,[42] who was the first to use mercurochrome intravenously on clinical cases, at the University of Pennsylvania, preceded this by the following animal experimentation. He estimated that in the human a dose of 5 mg. per kilogram of body weight would give a concentration of the dye in the blood of approximately 1 to 13,000. With defibrinated blood, he found mercurochrome at a concentration of 1 to 8000 killed hemolytic streptococci in forty minutes. At 1 to 16,000 there were two colonies of hemolytic streptococci from cultures prepared at one hour after inoculation. However, cultures taken at any time over an hour were sterile. Injected into the blood stream of normal rabbits mercurochrome produced no definite change in the leukocyte or differential count. To a rabbit he gave intravenously 5 mg. per kilo daily for three days with no resulting hemolysis nor change in leukocyte count. The next day no injection was made, after that 7 mg. per kilogram was injected every other day for three doses. Therefore, 10.6 cc. of 1 per cent was given in fourteen days to a rabbit weighing 2.4 kilograms. This resulted in no urinary change with the exception of occasionally a trace of albumin. He was unable to ever demonstrate mercury in the urine. The animals were then killed and found normal at necropsy. The bodies were macerated and examined for mercury with negative results.

In some control rabbits he produced a fatal Streptococcus septicemia. In others, which had received the same streptococcus injection, he later injected mercurochrome intravenously with a result that the animals recovered.

In a series reported by Freeman and Hoppe,[20] of 12 children with pneumonia, mercurochrome intravenously gave very fine results. Ten recovered and two died. They think these would have been fatal anyhow. Their theory is that mercurochrome leaves the blood by osmosis and incorporates itself in the lymph and tissue fluids.

Two dogs, one hour after being injected with the dye intravenously, were killed, the lungs removed, and their tissue juices

were squeezed out. One drop of the tissue juice was mixed with a standard loopful each of staphylococcus and streptococcus. Smears were made and incubated for twenty-four hours. Controls showed luxuriant growth but the bacterial suspension of tissue fluids showed only a few scattered colonies. They conclude that "the tissue fluids of the lungs, after intravenous injection of mercurochrome, are inhibitory to the growth of bacteria."

Young, Scott, and Hill[74] have recommended mercurochrome by mouth as a urinary and intestinal antiseptic. They say it is innocuous and causes little or no gastrointestinal disturbances until it has been taken in big doses for a week or more. Dosage of 900 mg. daily shows colorimetrically in the urine a dilution of between 1 to 30,000 and 1 to 40,000 and occasionally 1 to 15,000 to 1 to 20,000. At this strength urine is claimed to be bacteriostatic. The stools become deeply stained, almost brick-red in color, and the normal bacterial content may be greatly reduced. They suggest its use in colitis and possibly as a preparatory treatment for gastrointestinal operations.

Rosenthal and White[50] showed that considerable mercurochrome is eliminated through the bile. In two rabbits, there was an average biliary excretion of 25 per cent in one hour, and 44 per cent in the two hours following injection.

Hill and Scott[28] found it first appears in the bile of rabbits fifteen minutes after intravenous injection of 5 mg. per kilogram and is at the greatest concentration, that is, 1 to 5000 to 1 to 25,000, during the first two hours, and continues to be excreted at 1 to 8000 to 1 to 50,000 for the next two hours, and is entirely eliminated in twenty-four hours. By the mouth it appears in the bile in two hours, and in weaker concentration but of bacteriocidal strength. *In vitro* at 1 to 1000 in bile it will kill all the organisms tested but the Staphylococcus aureus in one hour, and at 1 to 5000 kills Bacillus typhosus in one hour. In five hours it killed all but Bacillus paratyphosus A, Comma bacillus, and Staphylococcus aureus at 1 to 25,000. For twenty-four hours at 1 to 50,000 to 1 to 100,000 it killed all but Staphylococcus aureus. Bile from rabbits which had previously been injected was inoculated with Bacillus typhosus. The bile was found bacteriocidal.

Bacillus typhosus was injected into the blood or gall bladder of rabbits. This produced cholecystitis. After single intravenous injections of 3 to 5 mg. of mercurochrome per kilogram, no organisms could be recovered from the bile. The controls were positive. Also bile was sterilized by giving 7.5 mg. per kilogram twice a day by mouth for 14 doses.

Unfavorable Evidence. After the favorable reports cited many patients had mercurochrome intravenously and the cases which had good results were promptly reported. This gave the impression that the drug would accomplish the miraculous, and it began

to be used indiscriminately for practically every type of infection. One great difficulty was that the literature looked as if most of the cases were simply snatched from the jaws of death. There were no controls and physicians were loath to report cases which received no benefit. However, in the last year there has been more of a note of pessimism and a suggestion that the drug may be actually dangerous.

St. George[56] reported 5 fatal cases of sepsis following abortion, in all of which mercurochrome was used intravenously. Autopsy in each showed intense nephritic and intestinal lesions. Chemical analysis of these viscera showed mercury in even larger amounts than was found in mercuric chloride poisoning. He concluded that the margin of safety between a therapeutic and toxic dose must be variable and small indeed, and that in 5 cases reported the mercurochrome probably contributed to death. In necropsies on cases which have received mercurochrome he has found 12 cases showing renal and colon involvement.

DeWitt[15] in 1920, showed that mercurochrome injected subcutaneously in guinea pigs would cause infiltration, induration, necrosis, and ulceration of tissues about the point of injection.

Rolnick,[49] on dogs, found that vasotomies with injection of mercurochrome of 2 or 3 per cent strength caused definite occlusion of the vas by scar tissue in 18 out of 20 dogs. The animals were all killed at ten days after the injection. The reaction varied from filling up the lumen with mercurochrome and detritus and destruction of the epithelium to complete occlusion. In 1 case, sections showed only scar tissue and no evidence of normal vas structure.

On dogs, Corper[11] injected mercurochrome at strengths varying from 0.01 per cent to 2 per cent intracutaneously, intratracheally, and into the pleura. Twenty-four hours after using 2 per cent intracutaneously, the skin had an orange mercurochrome color 1 to 1.5 cm. in diameter surrounded by a purple, hyperemic, slightly edematous border. At the fourth to seventh day ulceration occurred with sloughing of the involved skin area leaving a dark pink mercurochrome-colored floor of the ulcer and undermined edges. By the twelfth day the débris had been discharged, leaving granulation tissues. Healing was complete in three to five weeks. Using 1 per cent, the same lesion was produced, except that it was smaller; 0.5 per cent gave the same but still smaller. Injecting 0.2 cc. of 0.1 or 0.05 per cent, a slight pink skin and small area of edema and induration 3 to 4 mm. in diameter was produced for three to seven days. There was no ulceration and it was resorbed. No perceptible skin lesion was produced by injecting 0.01 per cent.

Endotracheally in 21 dogs, he found distinct lesions were produced in the lung with concentrations as low as 0.1 per cent. This varied from mild edematous and desquamative alveolitis to acute hemorrhagic pneumonia with focal abscess formation and tissue necrosis

at 1 to 2 per cent. Resolution may occur or a proliferative pneumonitis with granulation and scar tissue. *In vivo* mercurochrome had a preservative effect on red blood cells.

Intrapleurally pathologic changes were produced with concentrations as low as 0.1 per cent. This produced a transient, dry, fibrinous pleurisy. At 0.5 per cent to 2.0 per cent there was produced a hemorrhagic pleural exudate and acute hemorrhagic pneumonia which resembled that following endotracheal administration. He concluded that it is bad to treat empyema with mercurochrome above a strength of 0.1 per cent.

In the discussion of this paper, J. A. Kolmer, of Philadelphia, stated that in general drugs injected intrapleurally are 10 to 20 times more toxic per gram of body weight than when given intravenously.

Gatch, Trusler, and Owen[21] injected a group of animals intravenously with Staphylococcus aureus. All died. Then with the same injection of Staphylococcus aureus to another group, part were treated with mercurochrome intravenously. In none was the blood stream sterilized and all the treated, as well as the controls, died. Some of the controls outlived those treated with mercurochrome. They report 2 septicemia cases in humans, 1 of which had no mercurochrome, and made a remarkable cure; while the other had mercurochrome intravenously and died.

In testing its effect on tuberculosis, Corper, Mebel, and Silver,[12] working on rabbits, found that it did not affect the disease. In one group, the first mercurochrome intravenously was one hour after injecting the tubercle bacilli into the blood. They wished to get the effect before the bacilli lodged in the tissues and became intracellular. The mercurochrome was repeated daily for two weeks with no effect on the tuberculosis. A second group received daily mercurochrome for two weeks, beginning one week after infecting, and a third group began treatment the day after infecting the animals. The dosage was 5 mg. per kilogram and in none did it affect the disease. Also locally over 0.1 per cent causes a tissue reaction while to kill the tubercle bacillus it takes an exposure of 1 per cent for twenty-four hours.

DeWitt[16] finds that the tubercle bacillus is inhibited in the test tube by mercurochrome 1 to 10,000.

A startling article by Major John E. Walker[65] has recently been published. He showed experimentally that staphylococci and streptococci grow better in blood containing even 1 to 25,000 mercurochrome than in normal blood. As the concentration of mercurochrome increases, the growth in general becomes more profuse, reaching a maximum at 1 to 400 for the staphylococcus and 1 to 800 for the streptococcus. Thus the bactericidal power of mercurochrome is destroyed by blood, the effect seemingly being brought about by its injurious effect on the leukocytes. This is at

least a theoretical objection to its use intravenously. He states mercurochrome is hemolytic when added to washed red blood cells suspended in salt solution. The presence of serum exerts a marked protective action on the blood cells which probably explains why mercurochrome can be given in relatively large doses without causing hemolysis. The same action would seem to prevent any bactericidal effect. His experiments "indicate that, even in the presence of serum, mercurochrome is much more toxic for red blood cells than it is for bacteria." Major Walker states that he has been unable to correlate his experiments with those of Hill showing a bacteriostatic action of the blood following the injection of mercurochrome, or with those of Piper showing streptococci were killed by a dilution of 1 to 8000 in defibrinated blood. This work eliminates the question of the direct action of mercurochrome on bacteria in the blood stream. Also the possibility of damage through injury to the normal antibacterial properties of blood may be a real danger of the drug.

Intraperitoneal Injection. Johnson[32] reported the use of 10 cc. of 2 per cent mercurochrome solution in each of 5 cases of perforative appendicitis, 4 of which were closed without drainage. All of the cases recovered. However, there were no controls and every surgeon knows that most such cases will get well if no drug is used. After removing the appendix the peritoneum will usually take care of the remaining infection.

Last December we operated on a woman, aged forty-six years, for subacute salpingitis. In removing the tubes considerable pus was freed so as to come in contact with new areas for absorption. There was no damage done to the bowel that we could see. Twenty cubic centimeters of 1 per cent mercurochrome were poured into the peritoneal cavity and a rubber-tissue drain inserted. She had a very severe reaction with a weak irregular pulse, cyanosis, chill, and Cheyne-Stokes respiration lasting for several hours. The next day she passed gas through the abdominal wound which was followed soon by feces. Although there is a possibility the bowel was traumatized, we believe this fecal fistula as well as the very severe reaction were caused by the mercurochrome.

This case caused me to inject several dogs intraperitoneally with the dye at the Department of Experimental Surgery at the University of Nebraska College of Medicine. In all 9 were injected intraperitoneally, 8 of which received 5 mg. per kilogram of body weight, and the other 10 mg. per kilogram. All had severe reactions. These were more severe than the reactions in 5 others which had intravenous injections. Also 1 of the dogs which received 5 mg. per kilogram intraperitoneally died during the night following the injection. Autopsy showed many very much injected patches on the ileum.

Many of the animals were killed forty-five hours after injection

and both those injected intraperitoneally and those intravenously, showed marked congestion of the mucosa of the colon and some of the ileum; renal congestion, and in four there were renal abscesses, marked congestion of the lungs, and in many also congestion of the liver. These changes were noted both macroscopically and microscopically. No peritoneal adhesions were found.

Therefore, the mortality in dogs was 11 per cent. The case reported indicates it may cause a fecal fistula. Both dogs and the human had much more severe reactions than intravenous injection would give.

A Skin Disinfectant. Many cultural tests have been made by Scott and Hill[54] on the bactericidal properties of mercurochrome when applied to the skin. After considerable work they recommended the following: Place 2 gm. of mercurochrome in 35 cc. of distilled water, then add 55 cc. of 95 per cent alcohol and 10 cc. of acetone. The acetone increases its penetrability and causes it to dry faster. Tests showed it a better skin disinfectant, especially for staphylococcus, than tincture of iodin, picric acid, or Kalmerid (1 per cent solution of potassium mercuric iodid in 80 per cent acetone). The mercurochrome mixture and picric acid were found to penetrate the dermis better than does tincture of iodin or Kalmerid.

Tinker and Sutton[59] applied a 5 per cent mercurochrome solution in 50 per cent alcohol to the skin, and three minutes later made cultures. It was found to kill Staphylococcus albus and aureus, Bacillus coli, Streptococcus hemolyticus with broth culture, and vegetative anthrax. It did not kill Bacillus subtilis, Streptococcus hemolyticus in a blood-broth culture, Bacillus pyocyaneus, anthrax spores, Bacillus tetani, or Bacillus welchii. However, it is just as effective as a 5 per cent tincture of iodin. The best antiseptic they tested was acriflavin 5 per cent, in alcohol 50 per cent, but this is too expensive for general use.

Mayes[38] recommends injecting 4 per cent mercurochrome into the vagina during labor to reduce the chances of infection.

Mercurochrome stains may be removed from the skin[17] by rubbing with 2 per cent potassium permanganate, and then with 2 per cent oxalic acid solution. It may also be removed by Dakin's solution.

In 3 cases of normal humans, after painting a portion of the tongue with mercurochrome 10 per cent, Bloomfield[2] made cultures. He found the dye had no effect on a green streptococcus but inhibited all other organisms.

Effect in Edema. To test its effect in edema, Hirschfelder, Malmgren, and Creavy,[29] produced edema of the neck of rabbits by injecting 0.3 mg. of paraphenylendiamin per kilogram. Then 5 mg. of mercurochrome per kilogram was injected. They found that the dye penetrates the edema fluid and in thirty minutes reaches the concentration it has in blood plasma. However, even then it

is not bacteriostatic nor bactericidal for Bacillus coli or staphylococci. The conclusion is that it is unlikely to influence local and general infections clinically.

Use in Wounds. There are several reports of the use of the drug in infected wounds. However, one must remember its power of absorption. There have been many such cases in which stomatitis is produced. Therefore, in pouring it into a wound, or especially into a serous cavity, its dosage should be figured on the same basis as if used intravenously.

In gonorrhea the reports are conflicting.

Precipitation by Local Anesthesia. In a patient, Stolz[57] injected into a urinary bladder 30 cc. of procain followed in five minutes by 45 cc. of mercurochrome. There was no discomfort but three hours later the patient was unable to urinate. On catheterization numerous pieces of solidified mercurochrome came away.

Warren,[66] in the chemical laboratory of the American Medical Association, showed that many local anesthetics or alkaloids added to mercurochrome cause a precipitate. This accounts for the trouble in the case of Stolz.

Reaction of Body to Mercurochrome Intravenously. In patients with previously normal urine, the intravenous injection of mercurochrome may cause a transient albuminuria, occasionally some casts, but no red blood cells in the urine. At times there is a slight decrease in the phenolsulphonephthalein excretion but no significant change in the nonprotein nitrogen of the blood. That indicates a mild and transitory nephrosis without edema. In the blood there may be a temporary drop in the hemoglobin, possibly due to hemolysis. There is an occasional lowering of the red blood cell count, but no change in the leukocyte or differential count. There is no significant change in blood calcium, coagulation time, or in fibrinogen. Electrocardiograms show no change but a sinus tachycardia for a few hours after injection.

Conclusions. There is experimental evidence of the value of mercurochrome-220 soluble intravenously in the treatment of septicemia and other infections. Other equally convincing experimental results point to the fact that it is not bactericidal in blood, and that its use is not unattended by danger. Many clinical reports show miraculous cures, others have no benefit, and in some it has probably hastened death. Therefore, treatment with mercurochrome must still be considered in the experimental stage. Because of its dangers it should not be used indiscriminately and should be reserved for desperate cases.

Mercurochrome is dangerous intraperitoneally because of the local irritant action and because of the often very severe general reaction.

If used in wounds, sinuses, or serous cavities its dose should be limited to 5 mg. per kilogram of body weight, as it is easily absorbed, and if too much is used, it may lead to severe reaction or stomatitis.

The alcohol-acetone-aqueous solution of mercurochrome recommended by Scott and Hill[54] is a very satisfactory preoperative skin antiseptic. However, it should not be injected into the nose, urinary bladder, vagina, and so forth, along with a local anesthetic, as this will give a precipitate.

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MYOCARDIAL INSUFFICIENCY FOLLOWING ARTERIAL HYPERTENSION, ITS PREVENTION AND TREATMENT.

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Of the chronic diseases of later life, myocardial insufficiency is one of the most frequently encountered, and provides a larger number of deaths than any other sickness. It is preceded in the

great majority of cases by arterial hypertension. Little wonder, therefore, that public interest has been aroused in regard to this condition, and that research in this wide field of pathology is being actively encouraged. It is the aim, however, of this paper to show that with the knowledge already at our disposal it is possible to postpone indefinitely the onset of cardiac failure in the majority of patients with hypertension, and that it is further possible to produce very striking improvement in those patients in whom cardiac disability is already present.

While acute and chronic infections, valvular diseases and intoxications, as well as arterial hypertension, lead to myocardial insufficiency, space will permit a brief discussion of the last-mentioned only. Sir Clifford Allbutt[1] has defined the extreme figure for a normal blood pressure: Systolic, 140 (in spite of the age); diastolic, 90. Levels above these are pathognomonic of abnormal states of the cardiovascular system, and should be dealt with accordingly. The progressive tendency of a neglected hypertension is well known, and while the patient goes merrily along enjoying life, the physician alone knows that if no intercurrent accident intervenes, eventually before the normal span of life has elapsed angina, apoplexy or myocardial failure will result. A prophecy as to the particular outcome in the individual case can be based with some probability on the familial tendency. As time goes on we are more and more struck with the reality of predisposition by heredity. It is the exception rather than the rule to find that no immediate relative of the patient has died from or is suffering from ailments at once referable to the cardiovascular system.

The etiology of arterial hypertension has been receiving and is deserving of a great deal of attention. Many cases, especially of the essential hypertension (hyperpiesis) group, go unexplained outside of the belief that pathology remains from antecedent infection or intoxication. Evidence unquestionably points to infection or intoxications, the usual malefactors to be blamed for our unsolved problems. Until more is decided in regard to the etiological factor or factors, treatment must be directed along prophylactic lines, preventing infection and intoxication and controlling the hypertension with the best available means when once it has become established. In this way sequelæ otherwise inevitable may be avoided.

Owing to lack of symptoms, months and even years may elapse before an existing hypertension is discovered. If routine or insurance examinations have not been made the patient eventually finds his or her way to the physician, complaining of nervousness, periods of depression, vertigo, headache, feeling of fullness in the cranium, tinnitus, impaired vision (dimness, spots or total blindness), temporal thumping, occasional "clutching at the throat" sensation, cardiac palpitation and swelling of the legs. With more

marked renal involvement additional complaints are pallor, edema of the eyelids and face, particularly in the morning, dull, persistent headache, delayed speech and thought, foul breath, coated tongue, bad taste in the mouth, loss of appetite, nausea or vomiting and pains in the extremities.

For weeks, months and usually years the left ventricle has had excessive work to do. Hypertrophy with a corresponding loss of reserve has ensued. Changes in the walls of the vessels to the myocardium facilitate the progressiveness of the degenerative process. As the untreated hypertension increases, which it is wont to do, with the appearance and persistence of the above-mentioned symptoms, a limit is reached where the myocardial reserve is exhausted. At this point, we may have such extreme pressures as 290 systolic and 160 diastolic, a value not infrequently met with. To ascertain the myocardial reserve we can study the systolic pressure of such a case upon a slight exertion. If the pressure increases the limit has not been reached, but more commonly the blood pressure falls, signifying a defeated myocardium. Thus, with the transition from uncomplicated arterial hypertension to myocardial insufficiency, we usually have a lowering of the systolic pressure, an approximation of the systolic and diastolic pressures, or in other words a smaller "differential pressure," so-called by Allbutt[1] in preference to the misleading term "pulse pressure."

Coincidently with the defeat of the left ventricle, the symptoms change. The severe headaches become less as the blood pressure falls, the sense of fullness in the whole cranium disappears, nervousness is less marked, vertigo may be lessened or increased and the temporal thumping is abolished. The "new patient," so to speak, provides the clinical entity produced by prolonged overstrain of the myocardium, with complete utilization of the reserve force. The propelling force is insufficient; a slowing of the arterial circulation results; peripheral manifestations, such as hepatic and pulmonary congestion, appear; the veins become engorged; edema is prominent. In such a case, unless a complete anamnesis is taken, the preceding hypertension may be overlooked. This very fact partly explains why hypertension as a cause of myocardial insufficiency has received less attention than valvular, toxic and infectious causes. Fahr[2] has demonstrated the extreme frequency with which hypertension antedates myocardial failure. He claims that 75 per cent of so-called chronic myocarditis originates in this way. In substantiating his belief he states that of 142 cases which were diagnosed as myocardial insufficiency, 109 had had at some time during their hospital stay a systolic pressure of 170 or over and a diastolic of 100 or over. Even this is conservative, as in cases with more marked myocardial degeneration this pressure may have ceased to exist long before admission. Traube[3] and Sahli[4] report cases of hypertension resulting from myocardial failure, the expla-

nation being that there was a vasomotor disturbance following the asphyxia of the vasomotor center in the medulla. On the other hand, we have seen a number of cases of myocardial incompetence where one of the first signs of improvement was an increased blood pressure. This is probably not due to a disturbance of the vasomotor center, but to a return of myocardial power.

Prevention. To reduce the blood pressure to satisfactory levels is to prevent myocardial overstrain. This is probably the greatest problem in medicine today. A brief review of the more common treatments may be given at this point.

Vasodilators. Amyl nitrite or nitroglycerin is used with benefit in cases of extreme emergency. When relief is sought from violent headaches or nervousness, erythrol tetranitrate gives more satisfaction as it has the most abiding effect of all the vasodilator group. For such emergencies these drugs have a place in the treatment of hypertension, but as the effect is evanescent, continuous use is to be deprecated (Dally[5]).

Iodids. While these are indicated in cases of specific infection, they are considered actually harmful in others, as are bromides, owing to their property of interchanging with the chlorids (Allen[6]).

Calcium Salts and Atropin. Calcium salts and atropin, by mouth, have been advocated by Kylin,[7] and recommended for trial by Allbutt,[1] with a view to moderating a supposed vagus predominance over the sympathetic system.

Organ Extracts. These have on the whole been disappointing. Moorhead,[8] however, reports good results with corpus luteum extract with d'arsonvalization in climacteric cases. German workers (Blumenfeldt and Cohn,[9] from Kraus' Clinic) are claiming results with animasa, an extract from the intima and media from slaughtered animals.

Venesection. Venesection is unparalleled in its effectiveness for dealing with crises, such as angiospasms, acute pulmonary congestion and edema of the brain. To obtain an optimum fall in the blood pressure the withdrawal must be rapid. Blood-volume studies show that the total blood volume in hyperpietic patients is practically normal. This is confirmed by unpublished work of Scharf, Lundin and Wagner, verifying the clinical findings that venesection should be adopted with temporary relief in view only.

Lumbar Puncture. Lumbar puncture is efficacious in threatened apoplexy and in warding off or relieving uremic convulsions (Dally[5]).

High-frequency Electrical Treatments. These have many supporters for reducing blood pressure. Among these are Allbutt,[1] Cumberbatch,[10] Dally,[5] Humphries,[11] Brockbank[12] and Fontana.[13] While the length of the treatments and the strength of the current varied not only in the different clinics but with the individual patients, the results obtained by Roberts and Allbutt seem to have been satisfactory with only ten minutes of autocondensation

treatment daily. The fall in blood pressure is attributed to increased renal function. Our experience with baking, diathermia and autocondensation is limited, but during the past eighteen months we have seen no impression on any one hypertension, which had first proven refractory to a strict diet.

Tincture of Digitalis. This drug in large doses approaching those advocated by Eggleston[14] and Pardee[15] in cases of fibrillation, and in small doses when the diuretic effect alone is desired, is probably the most valuable pharmaceutical agent available. Caffein sodium benzoate, theocin, theophyllin, diuretin and other diuretics are used. When these are ineffective, euphyllin, then novasurol or salyrgan may still be tried. Euphyllin is a safe agent to aid in hurrying up the diuresis, but it is much less effective after the salt-free diet has been in use for any length of time, even before the chlorid excretion is reduced to the desired output. Novasurol, a double salt containing 33.9 per cent of mercury, has been shown by Saxl and Heilig[16] to be a powerful therapeutic agent in dealing with cardiac dropsy. This has been confirmed repeatedly by others.[17] Its use, however, is not without danger. It is contraindicated in the presence of extreme hypertension, impaired kidney function (unless it is a pure nephrosis) and where the myocardial decompensation is advanced to the point where the increased blood volume following the mobilization of edema fluid into the blood stream would make the load on the heart too great. Saxl overcame this by preparing the heart with digitalis or strophanthin, two or three days prior to the administration of the drug. Special care of the mouth is necessary to prevent a stomatitis. Colitis may be avoided by keeping the bowels open with castor oil. In the one case of myocardial decompensation where we used novasurol, after several weeks of a strict salt-free diet, there was a marked increase in the amount of chlorid excreted without any increase in the total volume of urine.

Diet. The protein intake has until recently been looked upon as a leading factor in the maintenance of the high pressure. Allbutt,[1] Volhard,[18] Mosenthal and Short,[19] Mosenthal,[20] Strouse and Kelman[21] and Allen[6] show in their work that no benefit accrues from protein restriction where there is no nitrogen retention.

Salt Restriction. This is observed by all in edema cases, but it is by no means so universally used for uncomplicated hypertension. Where salt-free diets are attempted we usually find that the total chlorid output is allowed to remain above 1 gm. To prescribe a salt-poor diet is one thing, but to keep the salt intake sufficiently low to reduce the twenty-four-hour chlorid excretion to 0.5 gm. (Whitehorn) or below is another. This is the standard set at this Institute, and it is responsible for the favorable statistics[22] recently published. The benefits are demonstrated partly by immediate results. In many cases there is a transformation within the first

few days or weeks, which is not explained by rest, psychic influence or other hypotheses. A demonstration is afforded by the permanent results (Allen[22]). Of 328 cases with systolic pressures of over 190 and diastolic over 110 under treatment in the past six years, the total mortality has been 43, or 13.1 per cent. This includes those who were unfaithful with their diet, those who had all degrees of kidney involvement and those who had suffered cerebral hemorrhage, as well as those who had no complications. Of this series, 19 per cent of the pressures were reduced to normal. In no case were there uncomfortable symptoms following the reduction. Symptoms with a falling blood pressure are more apt to be due to a failing myocardium.

In the treatment of myocardial insufficiency *rest* in the orthopneic position at the beginning is essential, especially if there is any pulmonary congestion or cyanosis indicating advanced exhaustion of the right heart. The blood pressure may still be high with a marked degree of myocardial decompensation. Where there is an acute pulmonary congestion venesection is of value. With relative weakness of the left ventricle there is the nocturnal cough with expectoration of tenacious sputum, followed by nights of orthopnea, with prolonged difficult expiration simulating asthma. It is a real edema of the lungs from the absorption of the edema and preedema fluids from dependent parts into the venous circulation, which takes place on lying down. Lichtwitz[23] points out that a dry diet postpones decompensation of the hypertrophic heart and is of inestimable value for nocturnal edema of the lungs. A considerable number of patients have on admission to the Institute complained of these asthma-like attacks; relief is obtained in a few days in almost every instance on a strict diet. By obviating thirst the salt-free diet has all the benefits of a dry diet and the simultaneous demineralization decreases the tendency to further fluid retention.

A detailed account of the value of the urine and blood analyses in pure hypertension or myocardial insufficiency here would be superfluous. A few of the more outstanding facts, however, deserve mention. A plasma chlorid* above 0.59 per cent (Whitehorn) in uncomplicated hypertension has provided a favorable prognosis in previously reported cases.[24] This has been continually proven since. On the other hand, a low percentage, below 0.56 per cent, has for the most part from the first promised more stubborn resistance to treatment. The chlorid level loses the greater part of its prognostic significance when edema, even in the slightest degree, is present. Altered permeability probably accounts for this. In these cases it is not unusual to see an actual increase in the plasma chlorid after the beginning of the salt-free diet.

* Figures referred to as chlorid represent sodium chlorid.

This fact has cast discredit on the value of the chlorid level as an indicator. It is wise to decide whether or not it has been influenced by the presence of edema. Actual pitting on pressure or visible edema we know discount its value. When the chlorid level fluctuates contrary to the above-mentioned rule, we must decide, before condemning it, whether an invisible edema or changes in the blood concentration could have played a part. Proof of the existence of an increased tissue fluid in the absence of pitting on pressure is shown by a definite loss of weight on a salt-free diet which is known to have a caloric value sufficient to at least maintain a constant body weight under normal conditions. This water loss is striking, in many cases with no apparent edema. Urine output never accounts for the total loss. Loss by way of the skin and lungs assumes fairly large proportions.

Urea. Allbutt[1] and Fishberg[25] have reported finding increased plasma urea without parallel renal involvement when myocardial decompensation existed. This is a rather constant finding in the more severe cases. Impaired renal circulation has been suggested as an explanation. Fishberg[26] has mentioned the frequency of increased uric acid in the hypertension group which ended in myocardial decompensation. This has been more constant than has the elevation of the urea in our series. In the light of Mann's[27] recent work with liver extirpation with a resulting increase of uric acid, room is left for hypotheses connecting liver function with arterial hypertension. The striking part of the urine picture is the relationship between the chlorid excretion and the blood pressure.

In conclusion one must say that a comparative statistical review of the treatments of arterial hypertension is impossible. Treatments which are the most popular are based oftentimes on observations made on single cases and not on large groups or over a great length of time. Both the tests of time and numbers show that the salt-free diet has proven extremely valuable as a measure in giving symptomatic relief and controlling the disorder.

For the treatment of myocardial insufficiency following hypertension a strictly salt-free diet has proven more effective than the laxer diets, where more emphasis has been laid on the pharmaceutical preparations employed.

Case Extracts. Case 2830.—A man, aged forty-eight years, was admitted May 30, and discharged, July 31, 1925. The symptoms were dyspnea dimness of vision, belching of gas and palpitation. Examination showed a blood pressure of 220 systolic and 100 diastolic, hydrothorax, dilated heart, marked ascites, enlarged liver, marked edema of scrotum, legs and ankles, decreased urine output, gain of weight, albuminuria. The past illnesses included scarlet fever, measles and mumps. His mother died of heart disease. The patient's arterial hypertension was known to be present three years; the myocardial insufficiency, eight months. Previous treatment included bedrest in hospital, daily purge, salt-poor, low-protein diet, diuretics and digitalis.

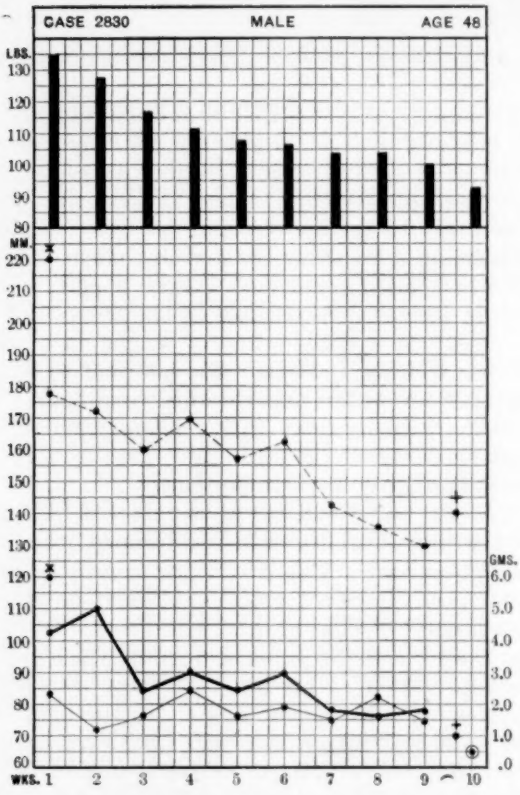

CHART I.—Key: Body weight: ▮. Systolic Pr: ----. Diastolic Pr.: ——. Urine chlorid: ——. Mm: millimeters of mercury. Lbs: pounds. Wks: weeks, highest and lowest. Syst. pressures: x, highest and lowest. Diast. pressures: ±. O: desired Sod. chlorid excretion.

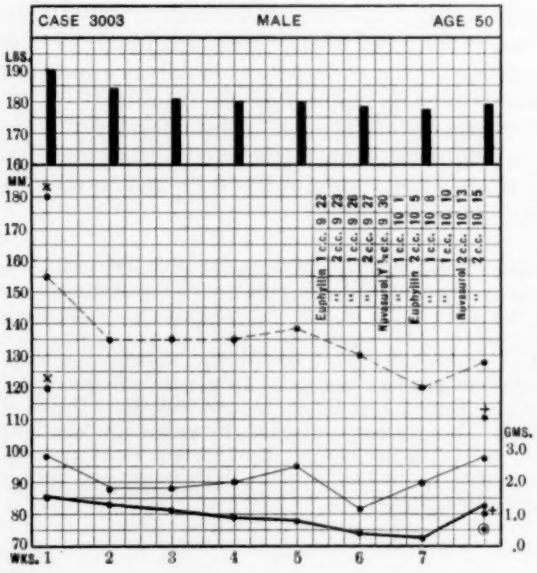

CHART II

CASE 3003.—A man, aged fifty years, was admitted, August 26, and discharged, October 17, 1925. The symptoms were dyspnea, weak spells and blurred vision. Examination showed puffiness of face, effusion in right pleural cavity, heart markedly enlarged, the blood pressure was 140 systolic and 100 diastolic, ascites was + 4, liver enlarged, extensive edema of the extremities, urine scant and containing albumin and granular casts. The patient's mother died of "dropsy." His arterial hypertension was discovered with the first signs of myocardial insufficiency two years prior to admission. Previous treatment included bed-rest, low-protein, restricted salt and Karell diets, as well as digitalis and diuretics.

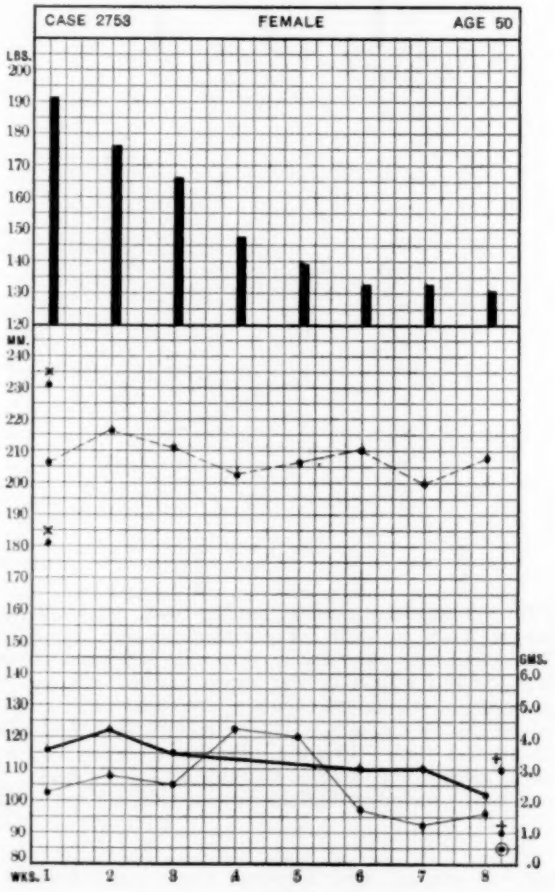

CHART III

CASE 2753.—A woman, aged fifty years of age, was admitted, April 8, and discharged, May 31, 1925. The symptoms were dyspnea and nocturnal asthma-like attacks. She had had three pregnancies, two normal and the last ending in miscarriage, attributed to fibroid uterus. Examination showed the face to be puffy and pallid, râles at both bases, heart and liver enlarged, blood pressure was 220 systolic and 130 diastolic, marked ascites,

prominent edema of the sacral area and extremities. Past illnesses included appendicitis, peritonitis, phlebitis of left femoral vein. Arterial hypertension was discovered at the time of onset of myocardial insufficiency in April, 1923. Previous treatment included intravenous "injections" on alternate days for past three months, bed-rest, low protein, restricted salt with diuretics.

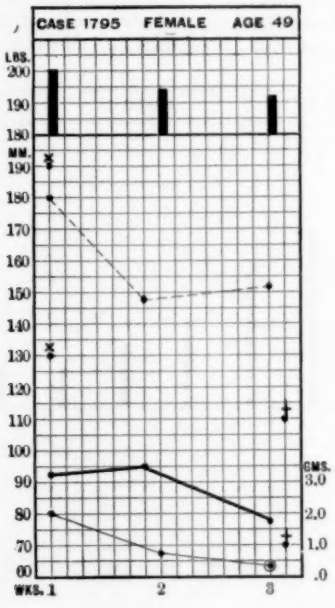

CHART IV

CASE 1795.—A woman, aged forty-nine years, was admitted, May 4, and discharged, May 24, 1924. The symptoms were dyspnea and palpitation. There had been one normal pregnancy at the age of twenty years. Examination showed edema of the lungs, marked cardiac, hepatic and splenic enlargement, prominent edema of extremities and a blood pressure of 182 systolic and 89 diastolic. The patient's father died following apoplexy, and a sister from "Bright's" disease. Arterial hypertension had been present twenty-five years; myocardial insufficiency, six months. Previous treatment included digitalis, low-protein, salt-poor diet and bed-rest.

CASE 958.—A woman, aged fifty-four years, was admitted, March 2, and discharged, April 11, 1922. The symptoms were dyspnea, dimness of vision, headaches, numbness of the right hand and chilly sensations. She had passed through two normal pregnancies. We found cyanosis, sclerosis of the retinal vessels, edema of the lungs, liver, heart and spleen enlarged, blood pressure was 210 systolic and 138 diastolic, marked ascites and edema of the extremities. Her mother and father both died following apoplexies and two of her immediate family have arterial hypertension. The duration of her arterial hypertension was ten years; myocardial insuffi-

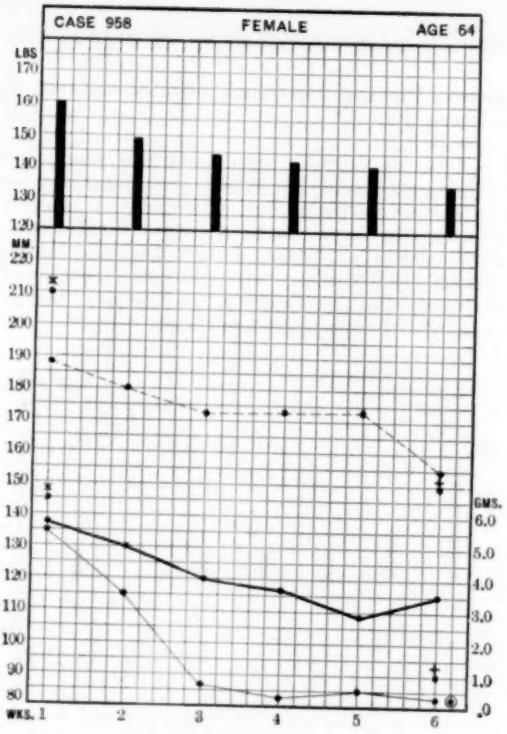

CHART V

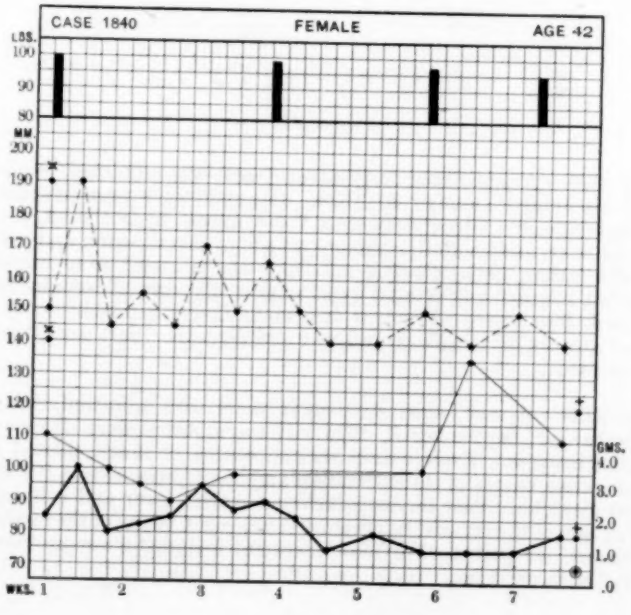

CHART VI

ciency, two years. Previous treatment included bed-rest, digitalis, low-protein and salt-poor diet.

Case 1840.—A single woman, aged forty-two years, was admitted, June 22, and discharged, June 29, 1924. Her symptoms were dyspnea, precordial pain and severe headaches. Examination showed an anxious facies, hydrothorax, edema of lungs, auricular fibrillation, enlargement of heart and liver, moderate ascites and marked edema; the blood pressure was 190 systolic and 129 diastolic. Arterial hypertension had been present twenty years; myocardial insufficiency, four years. Bed-rest, diuretics and digitalis comprised the previous treatment.

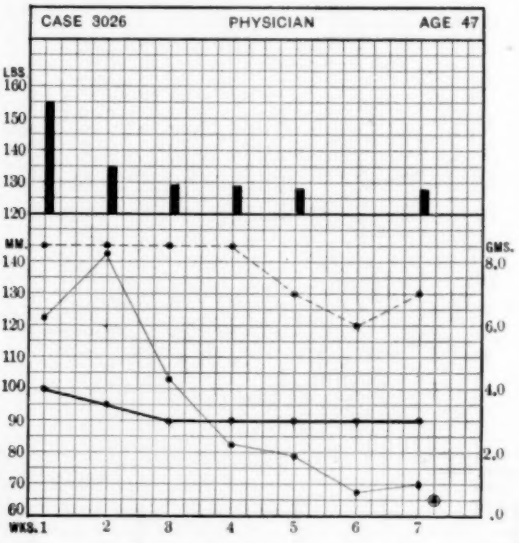

Chart VII

Case 3026.—A man, aged forty-seven years, was admitted, September 10, and discharged, October 20, 1925. His symptoms were dyspnea and precordial distress. Objectively there was cyanosis, hydrothorax, enlarged heart and liver, ascites and prominent edema of sacral region and extremities. His father died following apoplexy and a sister from eclampsia. He was not aware of any arterial hypertension; myocardial decompensation dates back four years. Previous treatment includes tonsillectomy after repeated attacks of tonsillitis, bed-rest and digitalis. Salt restriction was never advised.

Case 2959.—A man, aged sixty-eight years, was admitted, August 4, and discharged, September 8, 1925. His symptoms were dyspnea and precordial distress. Examination showed edema of lungs, dilated heart, marked ascites, edema of the extremities and blood pressure was 190 systolic and 140 diastolic. Past illnesses included scarlet fever and otitis media. The duration of the arterial hypertension was eight years; of the myocardial insufficiency, six weeks. Previous treatment included a low-protein, salt-poor diet with digitalis.

Case 2693.—A woman, aged fifty-five years, was admitted, November 7, and discharged, December 18, 1925. Her symptoms were dyspnea, palpitation, coldness of extremities, insomnia and gain of weight. She had passed through "several" normal pregnancies. Objectively there was cyanosis on the least exertion, a dilated heart, moderate ascites, liver

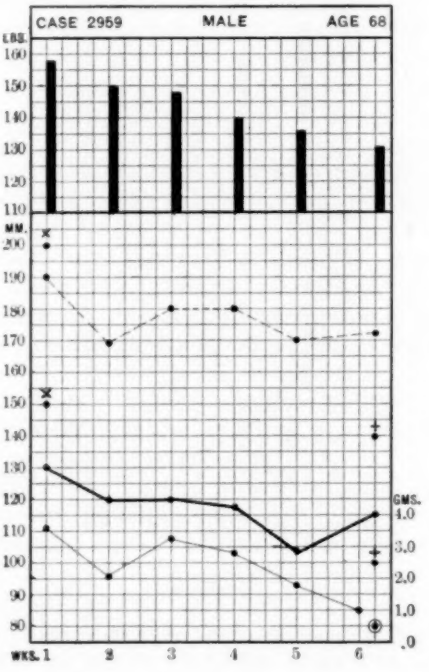

Chart VIII

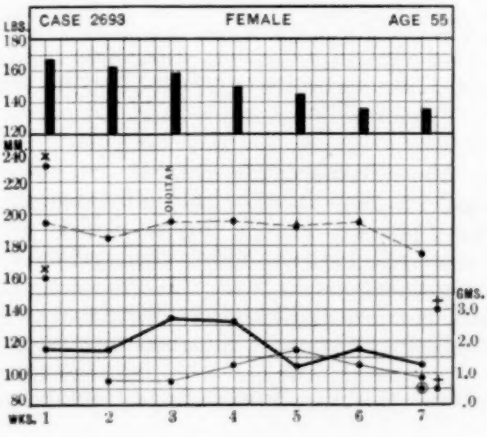

Chart IX

enlarged, tremendous edema of extremities; blood pressure, 230 systolic and 140 diastolic. Past illnesses included pneumonia. The duration of the hypertension was three years; decompensation, four months. Previous treatment included Karell diet repeatedly, low-protein and salt-poor diet.

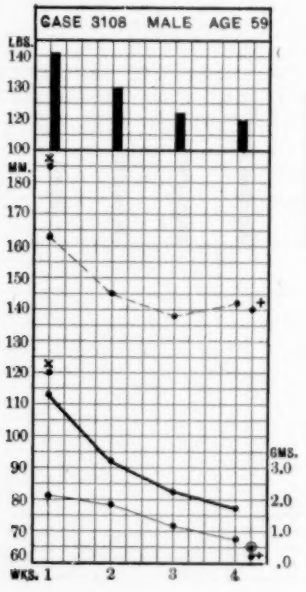

CHART X

CASE 3108.—A man, aged fifty-nine years, was admitted, November 23, and discharged, December 19, 1925. His symptoms were dyspnea, palpitation and weakness. Objectively, there was edema of lungs, a dilated heart, an enlarged liver, ascites of 4 +, marked edema of legs and ankles; blood pressure was 186 systolic and 140 diastolic. His father died from "dropsy" and his mother from "heart trouble." Past illnesses included pneumonia and indirect inguinal hernia (herniotomy was performed). The duration of the hypertension was two years; of the myocardial insufficiency, one year. Previous treatment included diuretics, digitalis, Karell and low-protein, salt-poor diets.

Discussion. The accompanying graphs* are self-explanatory. They are designed to show the relationship between the total urine chlorid, the blood pressure and the changes in body weight. They represent 10 cases selected from those which proved refractory to the standard treatments.

Daily variations are so great and deceiving that we have represented graphically *weekly averages* only, including body weight, sys-

* We are indebted to Miss Anne Powell, R.N., for assistance in computing the charts.

tolic and diastolic pressures and the total urine chlorid. A record is made, however, of the highest and lowest pressures obtained.

Loss of weight is prominent in each instance. This we attribute to water loss following a strictly salt-free diet. Undernutrition was not indicated in any one of these cases, so the caloric intake was never established below a maintenance level.

Effect on Blood Pressure. (*a*) *Systolic.* A decrease was obtained in every instance. A lowering to innocent levels was obtained in 7 cases (Cases 2830, 958, 3108, 1795, 1840, 3003, 3026), while 3 of them (Cases 2753, 2959, and 2693) still remained markedly above normal. In these 3 hope of ultimate favorable outcome could still be entertained, as the chlorid retention had not been entirely relieved. The chlorid output was still higher than could be accounted for in the diet. Case 1840 illustrates the increase of pressure with return of myocardial power, to decrease later when the effect of the diet was manifested. Also illustrated is the sudden increased urine chlorid after several weeks of treatment, a finding not uncommon in these cases. It is a favorable sign.

(*b*) *Diastolic.* Of more importance is the change in the diastolic pressure. While a decrease was obtained in every instance, satisfactory levels were assumed in six only.

Chlorids. While any edema, ascites or hydrothorax remained the output remained high (above 1 gm.). Improvement in the systolic and diastolic pressures before the chlorid excretion is reduced to 0.6 or 0.5 gm. in the twenty-four hours proved most favorable objectively, as well as subjectively. Resistance of the pressures to the effect of a diet which maintains the chlorid output below 0.5 gm. indicates vessel wall or kidney changes of extreme degree.

Progress Note. Three cases have been lost track of; 1 (Case 3026) died suddenly in January, 1926 (pulmonary embolus found at autopsy; the remaining 6 are active and maintaining control of their condition by adhering to the dietary régime outlined for them.

Treatment. (*a*) *Rest in Bed.* This was not necessary in any instance after six days' observation and treatment.

(*b*) *Medication.* Digitalis was continued in conjunction with the diet in all but 4 cases. We do not consider that the outcome was influenced by it, as all but Case 2693 had been on digitalis therapy until admitted. Euphyllin was used in Case 3003, with a sudden rise in the chlorid excretion followed by a decrease, making the week's average actually lower than the one previous. Novasurol was also administered with a resulting increased chlorid output, appreciably increasing the week's average without changing the volume of urine excreted. As the chlorid output increased, the diastolic pressure assumed a higher level.

(*c*) *Diet.* The diet was that with the lowest possible sodium-chlorid content, with protein restriction added only in Cases 2753 and 2693, where there was advanced renal involvement.

A few of the differences between a salt-poor and so-called salt-free diet may be mentioned to advantage. These differences explain the failure to get the chlorid output sufficiently low, the lack of results obtained with the more lax diet and the skepticism with which the diet is viewed by those who are satisfied with the salt-poor diet or who are unable to obtain the strict diet.

A diet aimed to obtain superlative results must be made up of foods with the lowest chlorid content. No salt or sodium bicarbonate is to be added to any foods either in the cooking or at the table. Allen[6] has pointed out the necessary limitations of the diet, excluding all foods high in salt, such as bacon, ham, corned beef, tongue, salted or dried fish and smoked or preserved meats; bakers' bread, cakes, canned fruits, vegetables and soups, as well as prepared cereals, such as corn flakes, are not permissible. milk and cheese have an incompatible chlorid content. Fruit in the form of apples, oranges and grapefruit, cereals as oatmeal, farina, shredded wheat, puffed rice with thick cream provide an available variety for breakfast. Eggs and salt-free meat, salt-free home-made bread with sweet butter and tea or coffee (in moderation) are permissible. Home-prepared, salt-free soups, fresh vegetables (canned vegetables must be brought to the boil three times and the water discarded each time to eliminate chlorids) may be added for lunch or supper. Horse radish, vinegar, pepper and other flavoring materials if properly used make the diet palatable. Medications, nasal sprays and mouth washes may be used only when the salt content is known to be minimal. The same precautions are to be exercised in the choice of solutions for douches and colonic irrigations.

Conclusion. Dietetic measures seem to provide the most powerful means of preventing and controlling myocardial insufficiency, which is secondary to arterial hypertension. They may and should be observed by the patient at home, after preliminary institutional instruction, when the supplementary measures, if any be used, are discontinued.

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MISTAKES IN DIAGNOSIS, AS SEEN IN A HOSPITAL FOR FAR-ADVANCED PULMONARY TUBERCULOSIS.

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From January 1, 1925, to March 8, 1926, there were admitted to the tuberculosis wards of the Baltimore City Hospitals, 460 patients, of which number 57, or a fraction over 12 per cent, were found to be nontuberculous.

It is interesting to learn of the ultimate diagnoses in these cases, and to review the symptoms and clinical findings, in an attempt at putting our finger on the weak link in the chain of evidence which resulted in the mistaken diagnosis of advanced phthisis. Some conclusions can be drawn from these data, particularly in regard to the circumstances under which it is unwise to make a diagnosis of tuberculosis. In arriving at the conclusion that tuberculosis did not exist, certain features of these cases appear of great significance; the type of fever, the character of the pulse, the clinical course, the persistence of negative sputum, and the satisfactory explanation of the patients' symptoms on demonstrable evidence of an existing disease other than tuberculosis.

The ultimate diagnoses in our 57 cases, listed in order of frequency, were as follows:

Diagnosis.	Cases.
Chronic bronchitis	10
Chronic lung abscess	8
Normal individuals	5
Bronchopneumonia	3
Bronchiectasis	3
Aneurysm of thoracic aorta	3
Syphilis of larynx and pharynx	3
Neurasthenia	2
Lobar pneumonia	2
Malignancy, secondary	2
Myocardial insufficiency	2
Malignancy, primary	1
Aortic insufficiency	1
Asthma	1
Infectious arthritis	1
Chancroid, with inguinal adenitis	1
Endocarditis, subacute bacterial	1
Hepatic abscess, with rupture into pleura	1
Malingerer	1
Mitral disease	1
Scarlet fever	1
Typhoid fever	1
Fracture of rib, with traumatic pneumothorax	1
No diagnosis established	2
Total	57

As the interest lies in the cases in which some reason for the diagnosis can be shown, all other cases, such as normal individuals, neurasthenia, malingering, scarlet fever, inguinal adenitis, arthritis, and the undetermined cases can be eliminated from our consideration.

Our observation of the remaining 44 cases resulted in 17 different diagnoses; in each, a reason for the mistaken diagnosis of tuberculosis can be considered and some diagnostic point of importance found omitted or overlooked.

Of symptoms complained of, cough and expectoration were present in all 17 conditions (44 patients). Hemoptysis occurred in 8

conditions, and 22 patients; in 13 conditions (35 patients), dyspnea was complained of; loss of weight occurred in 8 conditions (22 patients); fever in 6 conditions (16 patients). While 10 conditions (22 patients) showed increase in the pulse rate, only 5 (15 patients) had fever; one case with fever had no elevation in the pulse rate (typhoid). Weakness was rather generally complained of, being present in 13 conditions (36 patients). Pain was a symptom in 6 conditions (8 patients); sweats in 5 (14 patients); three conditions were associated with offensive sputum (12 patients), and two conditions (3 patients) with edema.

It would appear from this that certain symptoms suggested the diagnosis of tuberculosis, inasmuch as they occurred in the majority of conditions found present. Cough, expectoration, hemoptysis, weakness, tachycardia and loss of weight appear almost diagnostic in themselves when so grouped, but the clinical course, examination of the sputum, Roentgen ray, and the satisfactory explanation of the patient's symptoms on a demonstrable pathologic process other than tuberculosis proved that a diagnosis, based on symptoms alone, is not infallible. History, however, became of the greatest aid in arriving at a correct diagnosis, when the preceding health, the mode of onset, and the progression of symptoms were ascertained. Thus we found that every case of pneumonia was characterized by acute onset; that every case of abscess and bronchiectasis in our series was preceded by a pneumonia of atypical course or atypical termination; that every case of malignancy, excepting the primary one, was preceded by evidence of, or operation for, a malignancy elsewhere, and in our cardiac cases, dyspnea on exertion preceded cough, expectoration and hemoptysis by a considerable period. The character of dyspnea, cough and expectoration became of diagnostic value in bronchial asthma, lung abscess, and bronchiectasis. The history of chronic hoarseness, unassociated with pain, or with general symptoms suggestive of tuberculosis, was important in laryngeal syphilis.

The physical signs in 12 conditions (33 patients) were in the lower lobes, regardless of the character of the findings. Exceptions to this were found in laryngeal and pharyngeal syphilis, which showed no chest findings; in aneurysm; in 1 case of lung abscess occurring in an upper lobe; and in the primary malignancy, which occurred in an upper lobe. In the cases in which a wide distribution of physical signs were present, where apical rales were persistent, the signs were still more marked at the bases, so that the predominating findings were basilar. In 9 conditions (15 patients), demonstrable evidence of disease elsewhere than in the lung was found.

Of physical signs in the lungs, rales constituted the most uniform finding, being present in 13 conditions (35 patients). Of this number, only two showed rales in an upper lobe, with the lower

lobes free of abnormal signs. Three conditions (7 patients) showed no pulmonary signs.

The finding of rales in 13 different conditions makes very evident the fact that rales in themselves, like symptoms, are not typical nor diagnostic, of any one pulmonary condition or disease. The predominance of a basilar distribution of the signs in these cases is striking, occurring in 33 of the 35 patients showing lung signs.

Combining the most uniform symptoms and findings in these cases, it would appear that the wrong diagnosis of tuberculosis was made on symptoms of cough, expectoration, dyspnea, hemoptysis, weakness, and on the finding of rales in the chest. In the various conditions shown in our ultimate diagnoses, our speculation as to the reason for a diagnosis of tuberculosis made before admission to the hospital, and what appealed to us as the clinical diagnostic points overlooked, is briefly detailed as follows:

Chronic Bronchitis. Diagnosed tuberculosis because of chronic cough, expectoration, dyspnea, weakness, and rales in chest.

Diagnostic points overlooked were absence of all evidence to toxemia, basilar distribution of physical and Roentgen ray findings, absence of tubercle bacilli from sputum.

Abscess. Diagnosed tuberculosis because of cough, expectoration, hemoptysis, dyspnea, loss of weight, fever, sweats, and weakness, with evident signs in lung.

Diagnostic points overlooked were onset of symptoms following a pneumonia; rather copious sputum, definitely purulent and offensive; basilar distribution of physical signs; absence of tubercle bacilli from the sputum; clubbing of fingers.

Bronchopneumonia. Diagnosed tuberculosis because of cough, expectoration, hemoptysis, fever, and evident signs in chest.

Diagnostic points overlooked were acute onset; type of temperature, pulse and respirations; degree of toxicity of patient; basilar character of physical signs; leukocytosis; absence of tubercle bacilli from sputum; fever of comparatively short duration.

Bronchiectasis. Diagnosed as tuberculosis because of cough and expectoration, tendency to hemorrhage, evident signs in lung.

Diagnostic points overlooked were history of preceding pneumonia, copious offensive sputum, absence of general symptoms, basilar distribution of physical signs, absence of tubercle bacilli from sputum, marked clubbing of fingers.

Aneurysm. Diagnosed tuberculosis because of cough, hoarseness, pain in chest, dyspnea, streaked sputum, and possibility of dullness in upper chest. Diagnostic points overlooked were absence of toxemia, symptoms of mediastinal pressure; absence of lung signs; signs of lesion explaining patient's symptoms satisfactorily.

Laryngeal Syphilis. Diagnosed tuberculosis because of cough, hoarseness and expectoration.

Tabulation of symptoms in 44 cases.	Cough.	Expectoration.	Hemoptysis.	Dyspnea.	Loss of weight.	Fever.	Tachycardia.	Hoarseness.	Sweats.	Weakness.	Pain.	Fetid sputum.
Chronic bronchitis	X	X	..	X	?	..	..	..	..	X		
Abscess	X	X	X	X	X	X	X	..	X	X	X	X
Bronchopneumonia	X	X	X	X	..	X	X	..	..	X		
Bronchiectasis	X	X	X	X	..	..	..	..	..	..	..	X
Aneurysm	X	X	X	X	..	..	..	X	..	..	X	
Laryngeal syphilis	X	X	..	..	..	..	..	X				
Malignancy, secondary	X	X	X	..	X	..	X	..	..	X		
Myocardial insufficiency	X	X	..	X	..	..	X	..	..	X		
Malignancy, primary	X	X	..	..	X	..	X	..	..	X		
Lobar pneumonia	X	X	X	X	..	X	X	..	..	X	X	
Aortic regurgitation	X	X	..	X								
Bronchial asthma	X	X	..	X								
Endocarditis	X	X	..	X	X	X	X	..	X	X		
Hepatic abscess, with rupture into pleura	X	X	X	X	X	X	X	..	X	X	X	X
Mitral regurgitation	X	X	X	X	..	..	X	..	..	X		
Typhoid	X	X	..	..	X	X	..	..	X	X		
Traumatic pneumothorax	X	X	X	X	..	..	X	..	..	X		

Tabulation of clinical findings in 44 cases.	Upper lobe signs.	Lower lobe signs.	Septic temperature.	Continuous fever.	Tachycardia.	Dyspnea.	Leukocytosis.	Purulent expectoration.	Clubbing of fingers.	Demonstrable disease other than in lung.	Offensive odor to sputum.	Edema of ankles.
Chronic bronchitis	..	X	..	..	..	X						
Abscess (*a*)	..	X	X	..	X	X	X	X	X	..	X	
Bronchopneumonia	..	X	..	X	X	X	X					
Bronchiectasis	..	X	..	..	..	X	..	X	X			
Aneurysm (*b*)	..	..	..	..	..	X	..	..	..	X		
Laryngeal syphilis	..	..	..	..	..	..	..	..	..	X		
Malignancy, secondary	..	X	..	..	X	..	..	..	..	X		
Myocardial insufficiency	..	X	..	..	X	X	..	..	..	X	..	X
Malignancy, primary (*c*)	X	..	..	..	X							
Lobar pneumonia	..	X	..	X	X	X	X					
Aortic regurgitation	..	..	..	..	..	X	..	..	..	X		
Bronchial asthma	X	X	..	..	..	X						
Endocarditis	..	..	X	..	X	X	X	..	..	X		
Hepatic abscess with rupture into pleura (*d*)	..	X	X	..	X	X	X	X	X	X	X	
Mitral regurgitation	..	X	..	..	X	X	..	..	..	X	..	X
Typhoid	..	X	..	X	..	..	..	..	..	X		
Traumatic pneumothorax	X	X	..	..	X	X						

(*a*) Diagnosis in 1 case confirmed by autopsy.
(*b*) Diagnosis confirmed in 1 case by autopsy.
(*c*) Diagnosis made at autopsy.
(*d*) Diagnosis confirmed by autopsy.

Diagnostic points overlooked were absence of pain, absence of general symptoms, negative chest findings, negative result of sputum examination, demonstrable lesion in larynx, positive Wassermann reaction.

Malignancy. Diagnosed tuberculosis because of cough, expectoration, loss of weight, weakness, and evident signs in chest.

Diagnostic points overlooked were history of preceding neoplasm, absence of general symptoms of tuberculosis, atypical lung signs, negative result of examination of sputum, Roentgen ray evidence of metastasis. History and Roentgen ray of greatest diagnostic value.

Bronchial Asthma. Diagnosed as tuberculosis because of cough, dyspnea, expectoration and evident lung signs.

Diagnostic points overlooked were type and character of dyspnea, history of typical attacks, typical character of signs present, negative sputum.

Endocarditis. Diagnosed tuberculosis because of long-continued fever, sweats, loss of weight, possibility of rales, or signs of infarction in lung.

Diagnostic points overlooked were leukocytosis, demonstrable pathology in heart explaining patient's symptoms and the underlying cause of pulmonary findings, blood cultures, negative sputum.

Hepatic Abscess, with Rupture into Pleura and Bronchus. Diagnosed tuberculosis because of prolonged fever, cough, expectoration, loss of weight, sweats, hemoptysis, evident signs in chest. Diagnostic points overlooked were history of illness prior to onset of pulmonary symptoms, septic temperature, leukocytosis, offensive sputum, basilar distribution of physical signs, evidence of disease below diaphragm, clubbing of fingers, negative sputum.

Typhoid Fever. Diagnosed as tuberculosis because of symptoms of loss of weight, cough, weakness, rales in chest, prolonged fever.

Diagnostic points overlooked were continuous type of fever, bradycardia, rose spots, leukopenia, palpable spleen, blood culture or Widal reaction, basilar character of rales.

Traumatic Pneumothorax. Diagnosed as tuberculous pneumothorax, because of findings typical of the condition.

Diagnostic points overlooked were history of injury, explanation of cause of condition, by findings of fracture of rib.

Lobar Pneumonia. Diagnosed tuberculosis because of cough, expectoration, hemoptysis, pleuritic pain, fever, and evident signs in lung.

Diagnostic points overlooked were acute onset, continuous temperature with typical elevation in pulse and respiratory rate, marked toxicity of patient, lobar distribution of physical signs, leukocytosis, negative sputum, crisis.

Myocardial, Mitral and Aortic Insufficiency. Diagnosed tuberculosis because of symptoms of cough, expectoration, dyspnea, streaked sputum, and finding of rales in chest.

Diagnostic points overlooked were prominence of dyspnea as a symptom, absence of toxemia, basilar character of lung signs, typical findings of cardiac involvement explaining patient's symptoms and the occurrence of moisture in the lungs, presence of edema, negative sputum.

There are certain symptoms and findings in the foregoing cases which are deserving of some comment:

Dyspnea. Dyspnea in our experience, has not been a prominent feature in tuberculosis, unless some complication, such as effusion or pneumothorax, was present. The occurrence of an acute pleurisy may give rise to dyspnea from pain. Typical asthmatic attacks do not enter into the picture of tuberculosis.

Expectoration. The bringing up of copious amounts of sputum is unusual in tuberculosis.

Odor. Odor to the sputum is not present in tuberculosis, unless some septic or necrotizing process is complicating the condition.

Tachycardia. Tachycardia is the rule in tuberculosis; a slow pulse, while not conclusive, is most suggestive that active tuberculosis is not present.

Temperature. Height of temperature dependent upon the acuteness or the chronicity of the tuberculous lesion. Continuous temperature unusual, the afternoon rise being typical.

Clubbing of Fingers. This chronic pulmonary osteoarthropathy is constantly present in chronic septic infections in the lung, abscess or bronchiectasis, or chronic empyema, and is comparatively unusual in tuberculosis. Some curving of the nails is not infrequent in tuberculosis. Typical and marked clubbing of the fingers occurs in chronic ulcerative tuberculosis, in all probability due to secondary infection of the tuberculous cavity, so that the cause is again a septic process.

Tubercle Bacilli. Tubercle bacilli should be present in the sputum of patients suffering from advanced active tuberculosis. Negative results speak for inadequate search. No sputum should be reported negative, until careful search of the sediment of the digested total twenty-four-hour specimen has been made.

From the cases cited, it would appear unwise to make a diagnosis of advanced pulmonary tuberculosis:

1. When the illness is characterized by acute onset, and a high continuous temperature.
2. When the illness is characterized by a high temperature and a slow pulse.
3. When the history discloses that a malignancy is or has been present.

4. When the history shows dyspnea as the outstanding symptom, with evidence of cardiac disease demonstrable on examination.

5. When the history shows that copious amounts of offensive sputum are produced, and clubbing of the fingers is present.

6. When the physical signs are entirely, or predominatingly basilar, unless the sputum is positive.

7. When demonstrable evidence of a disease, other than tuberculosis, is present which fully and satisfactorily explains the patient's symptoms and clinical findings.

8. When the sputum is undoubtedly negative for tubercle bacilli.

Conclusion. The diagnosis of advanced pulmonary tuberculosis presents difficulties, which are often greater than those presented by incipient disease, and demands as complete and painstaking an effort on the part of the clinician as any problem in internal medicine, if serious mistakes are to be avoided.

PELLAGRA.*

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THE 56 cases in this series are of three types: Early cases in which symptoms and findings were trivial; late cases in which symptoms were severe, and cases in which the complication overshadowed the symptoms of pellagra. As a basis for discussion, illustrative cases will be summarized.

The course of a typical early or nonsevere attack is well shown by the following case:

Case Reports. CASE I.—A man, aged forty-one years, complained of constipation, and of mucus in his stools. In the summer time his hands were usually red and scaly, and occasionally he had sores in his mouth. His diet had consisted mostly of carbohydrates; he ate beef only once a week, because he thought meat was bad for him.

At the time of his examination, there was a dermatitis of the hands and face, and the skin of the hands and wrists were rough and scaly. No fissures were seen but there was a serpiginous

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border of marked hyperpigmentation surrounding areas almost vitiliginous in character. There was a mild secondary type of anemia. No free hydrochloric acid was found in the gastric content. Aspergillus, without photodynamic activity, was found in the feces. Proctoscopic examination revealed proctitis cystica. There were no definite neurologic findings, aside from slight mental depression.

The patient was given the "Asiatic pill," and his diet was gradually increased in quantity, and in protein and vitamin content. Response to treatment was prompt, and so far as known there has been no relapse.

CASE II.—A girl, aged nineteen years, had had severe diarrhea for three weeks. She was formerly vigorous and a hearty meat eater. The summer before her examination, she grew weak and spent much time outdoors lying in a hammock in the shade. She was "sunburned" to the point of vesiculation, and thereafter avoided the sunlight. As fall came on she grew stronger, but meat seemed to nauseate her. She grew pale and weak, sores appeared in her mouth, and her personality changed.

There was a moderate secondary anemia, and her blood pressure was low. She answered questions slowly, and her attention was poor. The stools contained much pus and blood, but no parasites were found. There was a typical pellagrous skin and mucous ulcers in the mouth. She was hospitalized and observed closely. Medication consisted of bismuth subgallate for the diarrhea, and Fowler's solution by mouth. Scraped raw beef and orange pulp including rind and seeds were given hourly. It became necessary, because of the patient's poor coöperation, to reinforce the food intake by rectal and intravenous injections of glucose. Her condition grew worse, and she was taken home by her parents. About one month later she died.

Several cases showing some of the various medical and surgical complications that may affect patients with pellagra, deserve epitomizing.

CASE III.—A man, aged sixty-seven years, had suffered severe gastric distress with vomiting and loss of weight for one year. Two months before he had become severely sunburned, although he was exposed to sunlight no more than usual. He has been on a diet of liquids, consisting mostly of milk, for some time. He was pale and emaciated, and had severe anemia.

Roentgen ray examination revealed an inoperable cancer of the stomach. The stools contained blood and pus, but no pathognomonic flora.

CASE IV.—A boy, aged ten years, had had "fits" and a skin rash. For three years he had suffered from a severe "eczema" which

would appear in June and last until November. For several months he had had extremely severe abdominal pains.

On examination a marked erythema on the dorsum of the hands, face and neck, and a severe ulcerating stomatitis of the buccal mucosa were noted. Whole oranges and scraped raw beef, $\frac{1}{4}$ gr. mercury with chalk were given three times a day, and the patient was sent home much improved, but with a grave prognosis. He died one year later.

CASE V.—A married man, aged forty-four years, had had, since 1918, periodic gastric pains relieved by vomiting. Two abdominal operations had been performed elsewhere, and evidently two gastroenterostomies completed, but he continued to lose weight and was still on a soft diet fairly complete, but containing no meat.

Examination revealed the typical "cravat" and dermatitis of pellagra. There was no free hydrochloric acid in the gastric content; but a secondary anemia, and a low blood pressure. The stools contained many Trichomonas hominis, and Entameba histolytica, but no fungi. The old gastroenterostomies were cut off and a pylorectomy performed for duodenal ulcer. A temporary jejunostomy for feeding into the jejunum rather than into the stomach was successful. On the removal of the tube, the wound closed spontaneously. The patient was put on a high-vitamin diet with a gradual increase in protein, and given the Asiatic pill. He gained 25 pounds and is now in normal condition.

Of the 56 patients, 30 were females and 26 males. The age varied from six and a half years to sixty-seven years; 5 patients were more than sixty years of age; 11 had severe complications; 8 were hospitalized for pellagra. Of these only 2 recovered, 1 was dismissed with no change in symptoms, and 5 died of the disease. In spite of the fact that the patients who were hospitalized were severely ill, and those who were ambulatory were generally in better condition, the definite impression exists that pellagrins do better when not hospitalized. Fifteen of the 56 patients definitely improved, 11 died, 3 of these from cancer.

The tendency of the unknown toxin of pellagra to express itself in the three great systems of ectodermal origin, the skin, alimentary tract, and the central nervous system, is obvious, and is manifested by the familiar diagnostic tripod of dermatitis, diarrhea, and dementia.

Skin Lesions. The skin lesions of pellagra have several definite characteristics. They usually occur where the sun strikes the skin, that is, the hands, wrists, neck, face, and, if thin hose are worn, occasionally ankles. They are conspicuously symmetric. The first stage is a severe erythema, the dermatitis passing from the acute stage with edema, erythema vesiculation and oozing, to the

FIG. 1.—Pellagra dermatitis of hands and wrists. Note the gauntlet formation of the pigmentation, the keratoses, and atrophy of the dorsum of one hand and the comparatively normal palm of the other.

FIG. 2.—Dermatitis occurring on the feet following exposure to sunlight.

FIG. 3.—Atrophic thinning and depigmentation with scaling after recurrent attacks of pellagra.

FIG. 4.—A case of trichophytic eczema for comparison. There is neither atrophy nor keratosis but thickening and lichenification due to chronic inflammation. The nails are also diseased.

chronic stage with thickening, scaling, pigmentation and hyperkeratosis and loss of elasticity. The margin of the dermatitis is sharply defined, and is especially noticeable between the fingers where the dorsal skin merges into the palmar covering. Cuff-like areas of hyperpigmentation occur which usually extend up the arms joining veritable gauntlets.

On the face the flush area is encroached on by a general erythema of dark hue. Since the malar eminences and the chin may be especially emphasized, the statement often appears in textbooks that the lesions may be discoid. This was not true in the cases in this series; close observation revealed that the entire flush area was involved. About the ala nasi and over the nose, in a sort of saddle, is a band of seborrheic dermatitis with marked sebaceous plugging of the follicles. These plugs are made up of sebum, easily expressed and quickly recurring.

The typical mucous membrane appearance was the beet-red denuded, edematous tongue with deep, distressing, dirty appearing aphthous ulcers at the tip and sides, and on the floor of the mouth. In some cases the pharynx and pillars were involved, and since dysphagia was a symptom; probably the esophageal lining. The gums bleed easily and appear spongy. Quite a number of the patients had apical abscesses, but this is not uncommon in patients in middle life. Ptyalism was not infrequent in cases of severe ulceration. About the genitals of two men, a rather scaly dermatitis was noted. One female had especially marked vaginitis, with lesions resembling the aphthous ulcers seen in the mouth in severe cases.

Alimentary Disturbances. The alimentary disturbances were many, and varied from slight indigestion to severe pyrosis, diarrhea and vomiting. The absence of free hydrochloric acid was a striking feature, and especially common in the presence of diarrhea. Givens found no relation between the absence of hydrochloric acid and the clinical symptoms, in the analyses of the gastric contents in 100 cases. The significant fact remains, however, that all pellagrins suffer from some abdominal complaint. Proctoscopic examination in 3 cases showed edema, erythema, and ulceration of the mucosa in 2 cases, and in 1, a condition diagnosed proctitis cystica. Stool examinations, in severe cases, usually revealed much blood and pus. In 1 case there was aspergillus, and in 2 cases Entameba histolytica. Monilia were found only once and were demonstrated to have no photodynamic action.

Neurologic Findings. Neurologic findings varied from a simple depression to the syndrome of combined lateral sclerosis in the chronic cases, and delirium and coma in the acute cases. Neurasthenic symptoms were common. Dread of food, and delusions, especially with regard to food, obsessions, repressions and muscular weakness, pains in the abdomen and extremities, headaches, backaches and vertigo were all present. These were only explained on the appear-

ance of the exanthem. The neurologic symptoms may be summarized as follows:

Neurasthenia, with trivial, yet distressing symptoms in themselves difficult to diagnose until the skin lesions appear; tabes, due to constant or recurrent attacks on the nervous tissue by the pellagra toxins, degenerations, with their stigmas of lost knee jerks, absence of sexual power, atony of the intestines, mental deteriorations, tremors, ataxis or loss of locomotion, and, finally, delirium or profound coma.

Features that automatically dismiss the consideration of other diseases are normal urine with low specific gravity, negative Wasserman reactions, low or subnormal temperature, low blood pressure readings (the highest was 135 systolic and 90 diastolic in a man aged sixty-one years) and the moderate secondary type of anemia.

Anemia. In most of the cases the anemia was moderate for such a severe disease. In the main the findings corresponded with those of Tirinder and Babcock, although no elaborate studies, such as those of Huck, were made. Any existing leukocytosis must be regarded as due to a complication such as pneumonia, and cystitis. The urine was usually normal, except for a rather low specific gravity. Only twice was there any trace of albumin.

Differential Diagnosis. Mistakes in the diagnosis of pellagra are apparently owing largely to the absence of suspicion on the part of the examiner and the overshadowing serious complications, rather than to adherence to a certain theory of etiology.

Pernicious Anemia. Severe cases of pellagra may easily be mistaken for pernicious anemia, and the skin lesions dismissed as eczema from poison oak. In fact these two diseases have so much in common that it is expected that the examiner's first reactions will be to suspect pernicious anemia. The shiny bald tongue, the vague gastroabdominal symptoms, the achlorhydria and diarrhea, accompanied with anemia, in the absence of skin lesions would make a diagnosis of pernicious anemia presumptive, if not probable.

Since pellagra may closely mimic such syndromes as neurasthenia, pernicious anemia, sprue and dementia precox, the value of an expert and careful examination of the skin becomes apparent. On the recognition of the pellagrous exanthem, all but a few diseases are promptly eliminated from the differential diagnosis. Ormsby has called attention to the importance of the correct interpretation of the skin lesions for accurate diagnosis.

Lupus Erythematosus (Discoid and Disseminate). Since both pellagra and lupus erythematosus are provoked to no uncertain degree by sunlight, and because of their more than superficial resemblance, lupus erythematosus of the usual discoid and the rarer disseminated types, should be differentiated. Indeed, as Goeckerman has said, some cases of the latter have probably been diagnosed as pellagra.

CUTANEOUS FINDINGS IN LUPUS ERYTHEMATOSUS AND PELLAGRA.

Lupus erythematosus.	*Pellagra.*
Few or many sharply defined discs or papules.	Lesions usually confined to flesh area of face, marked on chin, forehead and around the malar eminences.
Inflammatory reddish to purplish papules.	Dull red color.
Some scarring. Plugs are keratotic and are removed with overlying crust. No vesicles nor bullæ.	No scarring. Plugs soft and greasy, obviously seborrheic. No crusting. Vesicles in "wet" form. Lesions on skin rarely appear except on exposure to sun's rays.
Disseminate lupus erythematosus over the body.	

NONCUTANEOUS FINDINGS.

High fever.	Low or subnormal temperature.
Joint pains.	Rare joint pains.
No mental changes.	Severe mental changes.
Glands involved.	None.

Dermatitis Venenata. Dermatitis venenata has not the sharply defined hyperpigmented border, and either spontaneously subsides or persists as a chronic dermatitis with thickening, lichenification thickening and scaling. There are no vitiliginous changes, no hyperkeratosis nor atrophy.

Erythema Solare. Erythema solare does not occur suddenly in persons who have only been exposed to the sunlight for a short time, is more superficial, and a brighter red.

Trichophytosis. It was necessary to differentiate trichophytosis in one of the cases in the series, and this was promptly done by the demonstration of the organisms with potassium hydroxid preparation.

Acrodermatitis Chronica Atrophicans. This lesion is not usually in the part exposed to the sunlight, and is characterized by diffuse atrophy of the skin, and often a generalized telangiectasia. Senile skin is thin and atrophic with marked loss of the elastica. Keratoses may appear scattered on the dorsum of the hands and on removal may show early malignant changes. There is no marked involvement of the interdigital spaces with scaling and crusting around the knuckles.

Necropsy Findings. Necropsy was performed in 5 cases of the series. The important findings are as follows:

1. Changes in the intestinal tract. Atrophy and thinning of the intestinal wall with hyperemia and ulceration of the oral mucosa and of the lower part of the canal.

2. Abdominal pigmentary deposits, such as occur in senility, especially in ganglionic cells, muscles of the heart, the hepatic cells and the spleen.

3. Changes in the central nervous system. The principal finding in pellagra is atrophy of the lateral columns of the spinal cord.

The cord lesion may also implicate the posterior columns. Thus in 3 cases the lateral columns were found, clinically, to be affected.

Etiology. At present there are two distinct beliefs with regard to the etiology of pellagra. One, of which Goldberger is the ablest exponent, is that pellagra is a deficiency disease due to a low-protein diet, and the other, that pellagra is due to pathogenic intestinal flora.

The following case shows the occurrence of pellagra in a patient living on an exceptionally high-protein diet:

CASE VI.—A girl, aged twenty-one years, was operated on for tuberculous peritonitis in 1923. After the operation a fecal fistula developed. Because of the tuberculosis and its attendant wasting the patient was put on forced feedings of eggs, milk and meat. Sun baths were taken. The summer before examination she developed a distaste for meat, but conscientiously adhered to the diet ordered. In spite of the treatment a rough scaly dermatitis on the dorsum of both hands, with fissures and tenderness around the knuckles appeared. The cutaneous lesions disappeared in the fall, only to recur in the spring. On examination the typical chronic dermatitis of pellagra was found.

The "middle of the road" theory of Jobling and Arnold seems to us to be most appropriate at the present time. "Pellagra is not a deficiency disease, comparable to beriberi and scurvy, but one in which a definite intoxication arising most probably from the intestinal tract, forms the basis of the pathologic condition. This theory would explain the epidemiology of pellagra in patients with a high-protein diet, and would suggest that the peculiar skin changes may be caused by the action of sunlight on a subject rendered photosensitive by a substance elaborated by intestinal flora."

That pellagra is a deficiency disease comparable to beriberi or scurvy is not demonstrated in the cases in this series, since in many instances patients living on a high-protein diet had pellagra. On the other hand, the findings, on repeated stool examinations are distinctly disappointing. One patient only was found to harbor Monilia and Aspergillus, and two patients harbored Entameba histolytica. The work of Siler, Garrison and MacNeal on the Spartan Mill cases, showed definitely that pellagra was more prevalent in districts in which conditions were unsanitary.

Viswalingam has called attention to the fact that patients with pellagra do not automatically improve on diets containing more protein. It has also been found that hospital treatment is not indicated except in the most severe cases; in fact it would seem contraindicated in the ordinary case.

Jobling and Peterson found that a definite number of cases had occurred in individuals partaking of a wholesome varied diet.

Patients are ordinarily treated either by placing them in a hospital and abruptly changing the diet to one of high protein and vitamin, or they are kept ambulatory and a gradual change in diet instituted. Hourly feedings of whole oranges (seeds and rind) and broiled scraped beef steak are usually given. Mercury and arsenic in some form, such as mercury and chalk pills and the Asiatic pill may be used as an adjuvant. Ambulatory patients are simply given a list of high-protein foods and told to model their diet on it. Arsenic and mercury may also be given this type of patient.

Results of Treatment. Excluding patients in whom visceral cancer and esophageal obstruction were complications, those who were hospitalized and received intensive and abrupt dietary regime, showed the highest mortality. Patients with actual insanity or as in 1 case, epilepsy, aside from those whose mental changes were due to pellagra showed the next highest mortality.

On the other hand patients who were kept ambulatory, who made gradual and often slight changes in their diet, and who would consistently coöperate in attempts to recover, did markedly well.

Pellagra does not seem to be a contraindication to operation. Of course if intestinal parasites exist, appropriate treatment is indicated.

Conclusions. 1. Pellagra is probably not a simple deficiency disease like beriberi or scurvy.

2. While the causative agent may not be known, it is probably of an infectious nature, and gives rise to a substance which sensitizes the patient to sunlight.

3. Ambulatory patients do better outside the hospital, on a gradual readjustment of diet, than when hospitalized in a strenuous effort to effect a cure.

4. The necropsy findings are trivial for such a severe disease.

5. A diagnosis of the lesions of the skin is essential for a correct diagnosis of the disease.

6. Pellagra is not a "tropical" disease, but may appear anywhere at any age in either sex.

(I am indebted to Dr. Paul O'Leary for permission to publish this material and to Mrs. Maud Mellish for aid in preparing the manuscript.)

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THE RELATIVE VALUE OF THE ROENTGEN RAY AND PHYSICAL SIGNS IN THE DIAGNOSIS AND TREATMENT OF PULMONARY TUBERCULOSIS.

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There seems to be a great difference of opinion as to the relative value of the Roentgen ray and physical findings in the diagnosis of pulmonary tuberculosis. There should be no excuse for this attitude at this time when we consider the many illuminating articles by Dunham, Amberson and others during the past four or five years.

Many, who rank as tuberculosis specialists, pay little attention to the Roentgen ray in diagnosis and treatment and depend almost entirely on physical findings. Some of them even claim that, by studying the Roentgen ray, their judgment is warped and they are more apt to make mistakes. There is another class of internist, who goes to the other extreme. Not being well trained in the interpretation of physical findings, they place their entire reliance on the Roentgen ray, often not their own interpretation, but that of the roentgenologist. It is very evident that both of these views are extreme, and it will be the object of this paper to throw some light on the comparative value of these two methods which should not be antagonistic but should supplement each other.

The material for this study was obtained from the entrance examinations at U. S. Veterans' Hospital No. 50, Whipple Barracks, Arizona, from June, 1923, to August, 1924. The cases were not consecutive as, at various intervals, I was assigned to other duties.

Stereoroentgenograms were made on all patients on entrance, and both the physical examinations and Roentgen ray interpretations were made by the writer. However, the Roentgen ray readings of Dr. McWhirt, the hospital roentgenologist, were always consulted, and he was always ready with valuable advice in doubtful cases. Dr. Loewy, the Clinical Director, also gave much valuable assistance.

A few words in regard to how the diagnosis and comparisons were made: As a rule, the history was not considered of great value on account of the attitude of a large percentage of Veterans' Bureau patients. Experience has taught them what the history of a tuberculous patient should be, and our borderline cases, where our histories should be of great value, cannot be depended upon. Certain data were considered of great value, for instance, positive sputum tests; a parenchymal Roentgen ray lesion; pleurisy with effusion; medium rales and pulmonary hemorrhage. It was considered that any two of the above were sufficient basis for a definite diagnosis of pulmonary tuberculosis. As to physical findings, little attention was paid to bronchovesicular breathing and its variations, as these are characteristic of so many other pulmonary conditions. Slight dullness found in the upper part of the chest was also considered of doubtful significance, as thickened or rigid muscles and peribronchial thickening often produce changes in resonance. Therefore, the main reliance was placed on rales and definite dullness. In far advanced cases, the additional signs characteristic of cavitation, pneumothorax, and so on, were considered. In regard to the Roentgen ray interpretation, hilum infiltration and peribronchial thickening or infiltration were not considered of any significance as an indication of pulmonary tuberculosis, even when studding was present and the linear markings reached the periphery. Parenchymal infiltration alone was considered an indication of pulmonary tuberculosis. By parenchymal infiltration, we mean infiltration confined to an alveolus or group of alveoli, the infiltration being often confined to a series of secondary lobules due to the surrounding connective-tissue capsules. On account of the occasional shape of these areas as seen on the Roentgen ray plate, Dunham calls them fans, others speak of mottling, cirrhus clouding, and so on.

Dunham believes that thickened trunks and enlarged hilum shadows on the Roentgen ray plate can never be considered as being the result of tuberculosis, unless calcification or caseation are definitely shown to be present and even then are not in themselves evidence of active disease.

Colonel Bruns states, "We do not pay any attention to the peribronchial infiltration and only diagnose tuberculosis on parenchymal shadows. I believe that most of the mistakes are made by the roentgenologists who pay too much attention to the socalled peribronchial infiltration, and nowadays the roentgenologists, who have been interested in chest diagnosis for a great many years, have adopted the view that peribronchial infiltration, even though the lines extend to the periphery and even though they be beaded, is not indicative of clinical tuberculosis."[6]

The elimination of slight dullness and bronchovesicular breathing from our physical signs on one hand, and peribronchial thickening

on the other, makes our work of comparison more simple. In the average case, we need only compare the areas, over which we elicit definite dullness and rales, with the extent of the shadows on the film produced by the parenchymal infiltration.

In regard to the physical examination of the patient and the interpretation of the Roentgen ray it is important that they be made at the same time for the following reasons:

If the delay is too long between the making of the physical examination and the study of the roentgenograms, even though we have charted our findings, certain phases of the examination, such as the character of the rales and the grade of dullness, will not be so clearly fixed in our minds as when the examination was first made. We cannot, therefore, make the comparisons so intelligently, and we shall be much less accurate.

When the roentgenograms are read a few days or even a few hours after the physical examination has been made, the examiner loses the educational value of the comparison. It should always be the main object of the examiner to be able to judge, not the extent of the rales or dullness, but the character and extent of the underlying pathologic condition. When our patient is still in the room, if, following Aschoff, he appears to have a fibrous, a nodose or an exudative lesion, as seen by the Roentgen ray, we are able again to study the character of the rales, the breath sounds, and so on, and we shall thus become more expert in detecting and classifying tuberculous pathology.

It is a waste of valuable time to make the physical examination and then, after a day or two, read the Roentgen ray plates and finally correlate these with clinical symptoms and make a diagnosis. If we have all the data before us at the time of the first examination, we will be able to save at least 30 per cent of our time. The following, I believe, is the ideal routine: Stereoroentgenograms should always be made as soon as possible after the patient enters the hospital. These should be at hand when the physical examination is made. The history is at hand and the clinical symptoms studied. The examiner then makes the physical examination, charting his findings on chest diagrams in a book kept for that purpose. Before studying the roentgenograms, the examiner, with his physical findings in mind, should try to figure out the probable picture which will appear. On examining the negatives, he finds how nearly his mind picture was correct. The Roentgen ray findings are then charted on the opposite page of the book and the comparison made. Finally the patient is before us to be reëxamined, if necessary, so the Roentgen ray picture can better be checked with the physical findings. The graphic method of charging roentgenograms, as suggested by Webber, is very satisfactory.[5]

In our series, we made comparisons in 411 cases. Of this number, 245, or 60 per cent, we found to be tuberculous; 122, or 30 per cent,

we found to be nontuberculous; and 44, or 10 per cent, were classified as "observation" cases. Of the 44 observation cases, 18 were doubtful on account of an unexplainable elevation of temperature, and 26 were placed under observation on account of slight density (usually homogeneous) in one or both apices as seen by the Roentgen ray. Most of these cases, after being sent to the observation ward, were finally found to be nontuberculous, a few later showing definite tuberculosis. Of the 245 definitely tuberculous cases, 91 per cent, grossly or approximately, agreed in Roentgen ray and physical findings. That is, although the area of involvement did not always agree, the conclusions would be about the same as to whether a case should be classified as minimal, moderately advanced or far advanced. However, if we became more exact in our comparisons, we found that, in 124 cases, or 50 per cent, the area of involvement, as shown by the Roentgen ray and physical findings, was quite definitely the same. In 88, or 36 per cent, the Roentgen ray showed more involvement, and in 12 cases, or 5 per cent, the physical signs predominated. In 17 cases, or 7 per cent, there was Roentgen ray evidence of disease but no definite physical signs, while in 4, or about 1½ per cent, there were physical signs but no demonstrable Roentgen ray findings. In 11 per cent of the cases, the Roentgen ray showed unmistakable involvement of the second apex, which was not shown by physical findings.

In the series, cavitation was found in 90 cases, or 36 per cent. Of these cases 99 per cent were demonstrated by the Roentgen ray, while only 20 per cent were shown by physical signs alone. In 1 case only were there fairly definite signs of cavitation which were not shown by the Roentgen ray.

Comparison of cases having a Roentgen ray lesion and definite physical signs with those having a positive sputum is interesting:

Of the 245 definitely tuberculous cases, 163, or 66 per cent, had positive sputum. Of the 224 cases having both Roentgen ray lesion and medium rales, 69 per cent had positive sputum. Of the 17 cases with a parenchymal Roentgen ray lesion but no physical signs, 53 per cent showed a positive sputum. Of the cases showing physical signs but no Roentgen ray findings, all had negative sputum. Of the 140 cases showing neither physical signs nor Roentgen ray findings, none had positive sputum.

Definite constitutional symptoms, such as elevation of temperature and rapid pulse, were present in 48 per cent of the tuberculous cases. If we had made note of such constitutional symptoms, such as malaise, nervousness, insomnia and irritability, the percentage would, no doubt, have been much higher.

The comparison, between cases showing only peribronchial thickening and those showing parenchymal infiltration, as to the presence or absence of rales, is significant:

In only 1.6 per cent of cases showing peribronchial thickening

alone, were rales found, while they were found in 93 per cent of cases showing parenchymal lesions. Again, positive sputum was not found in any case showing peribronchial thickening alone, while it was found in 68 per cent of the cases showing parenchymal lesions.

It is in helping to determine the actual lesions present in the lung that the Roentgen ray has its greatest value. In order to treat our cases properly, it is not enough to have made a diagnosis, it is not enough to know that our patient has rales and bronchovesicular breathing over certain areas. The clinician will be most successful who is able to determine the existing pathologic condition of the lungs most accurately. He must be able to say, if we use Aschoff's classification, that there is a nodose lesion involving the upper lobe of the right lung or an exudative lesion of the lower lobe of the left lung.

Some clinicians endeavor to determine the existing lung lesions from the constitutional symptoms and clinical findings, but their results are very inaccurate.

Constitutional symptoms may tell us something, especially as to allergy or perifocal reaction, but they give us a doubtful clue as to the nature or extent of the lesion.

Physical findings sometimes depict fairly accurately the extent of the lesion, but they not infrequently fail us if we attempt to determine from them the pathologic picture or the presence of activity.

Let us take the rales which are considered the most characteristic sign of pulmonary tuberculosis.

This type, called by Bruns a parenchymal rale, is a medium rale often heard at the end of inspiration but usually at the beginning of inspiration following expiratory cough. These rales are very uniform in size; they occur in showers; they burst near the ear, are crackling in character and are persistently heard, month after month, over the same area.

Many of us, who have been in tuberculosis work for a long time, have been greatly puzzled in regard to these rales. Some years ago, I became very pessimistic as to the ultimate outcome of tuberculous cases. Many patients were observed where, although they faithfully carried out instructions, the rales remained the same, month after month and year after year; their general condition was good; there was but little cough or expectoration and very slight or no constitutional symptoms. We called these cases stationary active, because the rale did not change. We know now that the term "stationary active" is a misnomer, that it has been used for a class of case that was for the most part quiescent, apparently arrested or arrested and was called active only because of the persistence of rales. If roentgenograms had been taken at two- or three-month intervals and careful comparisons made, it would have been found that many were not stationary and would have shown marked retro-

gression of the pathologic lesion or only a fibrosis in spite of the continuance of the rales.

It was not until we heard the lectures by Colonel Bruns[6] at Fitzsimmons Hospital, in 1923, that the true mechanism of these rales was suggested to us. He states that the rales usually considered most characteristic of pulmonary tuberculosis were not due, as generally supposed, to moisture in the alveoli and small bronchi, but were atelectatic rales, the collapse of the parenchymal alveoli being caused, as expressed by Colonel Bruns, by "An exudate or infiltration in a neighboring lobule, to the constriction or contraction of areas of fibrous induration or to the partial occlusion of bronchioles by the pressure of inflammatory tissue or by the constriction of fibrous bonds."[6]

In a recent article in the *Journal of the American Medical Association*. Colonel Bruns gives in detail his experiments in determining the mechanism of these rales, which he designates as parenchymal rales. His statements are most convincing, and his publication should be considered one of the monuments of progress in scientific medicine.

In speaking of these rales, he states as follows. They are "localized and constant regardless of the quantity of the patient's expectoration. They remain unchanged, irrespective of how much the patient coughs or raises during the examination. A cough is usually necessary to elicit them. They are fine or medium, but they are uniform in size and occur in showers at the same phase of respiration. They are encountered in all the pathologic-anatomic types of tuberculosis. The lesions may caseate and progress; they may fibrose and heal; perifocal reaction may develop and subside; pleural adhesions may be present or absent; the patient may have severe constitutional symptoms or none at all; he may have considerable cough with profuse expectoration or no cough and no expectoration; the Roentgen ray may show any type of tuberculosis, and the involvement may be dense or it may be difficult to detect; still these rales remain unchanged and can persist indefinitely. It is true that, not infrequently, in time, as the lesions clear up and heal, the rales disappear, but we see many cases in which they persist after the patient has become cured, and the Roentgen ray reveals fibrous tuberculosis."[9]

The rales so characteristic of pulmonary tuberculosis are not, therefore, caused by moisture in the alveoli and small bronchioles, as formerly supposed, but are produced in partially collapsed, more or less normal lung tissue, such collapse being produced by the adjoining tuberculous infiltration.

It is very evident that rales, the most characteristic sign of tuberculosis, are of practically no value in depicting lung pathology; whether a lesion is caseous or fibrous, active or arrested, the rales may persist and retain the same characteristics.

Constitutional symptoms and physical signs being so inadequate in revealing to us lung pathology, let us turn to the Roentgen ray. Here, we have portrayed before our eyes the pathologic changes in differences in density.

To take advantage of this revelation, we must know that serous infiltration, cellular infiltration, caseation, fibrous induration and calcification cast shadows of increasing density in the order named. We must also know the minute anatomy of the lung, have a knowledge of the pathology of tuberculosis, an understanding of allergy and immunity in tuberculosis, as revealed by Koch, Krause and others, a thorough understanding of clinical tuberculosis, and last, a knowledge of the roentgenoscopic pathology of the lungs.

In Colonel Bruns' statement: "Of all methods at our disposal, the Roentgen ray is the most important one factor in placing before us the pathologic condition of the lungs in pulmonary tuberculosis,"[6] we have the opinion of not only a roentgenologist but one who is, above all, a clinician and an expert in the methods of physical diagnosis.

The great importance of the value of the Roentgen ray in showing the pathologic condition is very aptly stated by Dunham and Skavlem: "Armed with the knowledge gained from experimental studies, the pathologist lays bare the dead lungs on the autopsy table and tells us what has happened. Armed with the same knowledge, it is possible for the trained observer to lay here the living lungs on the Roentgen ray plate and tell us what has happened, what is happening and what probably will happen. The use of the Roentgen ray in the diagnosis of pulmonary tuberculosis is firmly established. Its value does not stop here, for it gives us the means of studying the disease as a scientific problem in its own unfortunate host. Lung pathology was taught us by the dissection of the dead, but now the progressive investigator is viewing his postmortem findings largely as a confirmation of his observations and predictions made from a Roentgen ray plate."

This paper would not be complete without a word as to the comparative value of the Roentgen ray and physical signs in determining activity. Various authors speak of different kinds of activity. They speak of constitutional activity indicated by fever, rapid pulse, malaise, and so on, clinical activity indicated by rales, and pathologic* activity as shown by perifocal reaction or the actual progression of the pathologic process. It is clear that pathologic activity must always be present in order to have constitutional or clinical activity. On the other hand, there may be a continuous extension of the process in the lungs with only slight elevation of temperature and pulse, and without increase of the discernible area of rales. Rales should never be considered necessarily a sign of

* The use of this term as opposed to clinical and constitutional would seem so misleading that it had better be discarded or replaced.—EDITORS.

activity. It is true, rales are usually present when activity exists, but they are probably more often present when there is no activity. The presence of fever, rapid pulse, and so forth is strong, positive evidence that activity exists, but, when these are not present, the negative evidence is not so strong, for pathologic activity may still exist. This can only be determined by the Roengten ray and in no other way, that is, by observing in serial roentgenograms definite changes showing the progression of the disease, as expressed by Amberson in the following paragraph:

"When at varying intervals serial pictures are made and these show a definite extension of the disease, pathologic activity is established. But to look at a single isolated picture of a diseased lung and to flatly diagnose activity is thoroughly unscientific and certain to invite error in many cases."[2]

The fact, that pathologic activity may exist without constitutional symptoms, is of great practical value in the treatment of our cases. Although constitutional symptoms should be our main reliance in determining activity, it is never safe in an apparently quiescent case to start exercise, heliotherapy or tuberculin without checking up frequently with the Roentgen ray for the presence of pathologic activity as demonstrated by an increase in mottling or a perifocal reaction.

Granted that pathologic findings appear first in the lungs, before constitutional symptoms or rales appear, can such findings be demonstrated by the Roentgen ray before constitutional symptoms or rales appear? In other words, which appear first, rales, constitutional symptoms or a parenchymal Roentgen ray lesion? There is considerable difference of opinion in regard to this question. The comparison made and described above throws but little light on this subject, as early cases were very limited and we did not have the opportunity for their continuous study. The following quotations are to the point: Barnes states, "The number of positive sputum cases where, over areas showing rales, the Roentgen ray findings are for a time negative but later positive, indicating a primary failure of the Roentgen ray to find the lesion, is small but probably not more than 2 per cent." Amberson says: "We have watched in a series of pictures undoubted, yet very slight progression of disease insufficient to produce a definite change in physical signs, but accompanied by symptoms of clinical activity that were unmistakable. Often, the syndrome has not included fever or other of the more startling manifestations which are later evidence of a reaction of increased intensity; instead, the patient may have mentioned only the vague sensation of nervousness, unaccustomed irritability, anorexia, insomnia or malaise. On such occasions, our practice is to go through the routine physical examination, often without obtaining much helpful information, and it is with greater hope of discovering a reason that we compare a new roentgenogram of the

lungs with the preceding series. In a very large percentage of cases, we find some tangible underlying cause, such as a definite increase in perifocal inflammation or new areas of mottling."

We see from the above that, although Amberson, in many cases, was unable to account for constitutional symptoms by a physical examination, nothing new being found, the Roentgen ray showed him definite progression of the disease. In other words, he was able to detect mottling and perifocal reaction in the roentgenograms before physical signs made their appearance.

To recapitulate briefly, we have shown that the Roentgen ray is at least of equal value to physical findings in making our diagnosis; second, we have tried to show that the Roentgen ray is of much greater value than physical findings in determining the existing pathologic condition of the lungs; last, we wish to emphasize the fact that the Roentgen ray has its greatest value in the routine care of our patients.

It is not only necessary that we acquire an exact picture of the lung lesions present at the beginning of treatment, but, to attain the best results, we must determine each step in the change of the pathologic picture as it takes place.

Constitutional symptoms and physical signs often deceive us as to the progress of our cases, and, if we depend on them alone, we shall often be misled. It is not unusual to see tuberculous lesions retrogress when constitutional symptoms still persist, to see remarkable clearing and absorption of the lesion with no change in the rales, to see cavity formation occur with no characteristic physical signs making their appearance, to see marked diminution in the size of the cavities without change in physical signs and so on.

Our study of physical signs and constitutional symptoms should always be supplemented by the careful study of serial roentgenograms taken at from two- to four-month intervals, according to the type of case. By this method, we can determine pathologic changes very accurately. The increase or decrease in the size of cavities can be measured, the occurrence of an extension and its absorption are seen by new areas of mottling and their later disappearance. Still further by these comparisons, we can tell when allergy increases or decreases by the appearance and disappearance of the perifocal reaction, when immunity is deficient by the characteristic picture of caseation and softening, and when immunity is present by fibrous induration.

Amberson has perhaps stressed the importance of these serial roentgenograms more than any other writer. The following quotations from one of his recent articles are much to the point: "By means of serial roentgenograms, the mutations of destruction and repair may be depicted at desired intervals for months or years. The method has been put to use with great advantage in the study of such respiratory infections as pneumonia, but the roentgenologist

has lagged in appreciating its applicability in tuberculosis, largely because of the length of time of observation necessary to note the gradual change. This should not be a hindrance in sanatoria where patients reside for long periods, and the time is at hand when the competent internist must be a master of the roentgenoscopic pathology of the lungs."[3]

It is most urgent that every tuberculosis specialist should know how to interpret the Roentgen ray and have a knowledge of pulmonary roentgenoscopic pathology. We know that rales are often of doubtful significance unless they are checked by the Roentgen ray. Further, it is not enough that the clinician should read the interpretation by the roentgenologist. When making a physical examination, the clinician is not satisfied to take some one else's findings; he prefers to make his own examination. It is even more important, considering the great value of the Roentgen ray, that he make his own roentgenoscopic interpretations, an expert roentgenologist being always available as a consultant.

In order that hospital staffs may be effectively trained in roentgenoscopic pathology, it is very urgent that advantage be taken at all necropsies of the opportunity to compare the Roentgen picture with the pathologic findings. Postmortem roentgenograms should be taken as a routine.

In this connection, the importance of the adoption of a pathologic-anatomic classification of pulmonary tuberculosis by tuberculosis hospitals is apparent. Such a classification is not only extremely important in teaching us tuberculous and roentgenoscopic pathology, but it affords a common nomenclature for the clinician, roentgenologist and pathologist, each of whom, using the same terms, makes his description comprehensible to all. A modification of Aschoff's classification, used at Fitzsimmons Hospital, admirably serves such a purpose:

Fibrous

Nodose { Discrete / Confluent } Productive types

Lobular pneumonia / Lobar pneumonia } Exudative types

Miliary — Productive or exudative

Each of the above types presents its own pathology, each presents a different roentgenoscopic picture and, to some extent, each presents its characteristic physical signs and symptoms. The roentgenologist may, during the life of the patient, interpret the Roentgen ray findings and declare the roentgenoscopic pathology present in terms of the above classification; the clinician, by studying the physical signs and symptoms, together with the Roentgen findings, may give his idea as to the probable pathology present in

the same terms, while, after the death of the patient, the pathologist, by using the same classification, expresses his findings also in the same terms, thus making the descriptions and comparisons uniform.

In this paper, we have tried to make a fair comparison of the Roentgen ray and physical signs. It is clear that the two methods are not antagonistic. They supplement each other, and it is not true, as stated by one writer, that many mistakes are made because too much attention is paid to the Roentgen ray. It *is* true, however, that mistake after mistake is made because the Roentgen ray is entirely ignored, not carefully studied or the roentgenologist's report only read and not understood.

It is also often a question of interpretation. In many instances, those who deprecate the Roentgen ray are addicted to wrong methods of interpretation. They still consider thickened and beaded trunks which reach the periphery or calcified areas in the hilum as evidence of pulmonary tuberculosis. Others discard the Roentgen ray as valueless because they sometimes find rales accompanied by negative roentgenograms, not deeming it possible that the rales were wrongly interpreted.

Proper interpretation, therefore, must be striven for. If we properly interpret the constitutional symptoms, the physical signs and especially the Roentgen findings and study all carefully, as well as the history, only then will we have reached a degree of accuracy which will do justice to our patients.

Summary and Conclusions. 1. From a study of 411 cases, 60 per cent of which were found to be tuberculous we believe that the Roentgen ray is the most important means of determining the existing pathologic condition of the lungs.

2. A parenchymal Roentgen ray lesion, without physical signs, is of great significance, for 53 per cent of such cases showed positive sputum.

3. Physical signs without a parenchymal Roentgen ray lesion are of very doubtful significance, for all had a negative sputum.

4. Peribronchial infiltration, as seen by the Roentgen ray, is of no importance in diagnosing pulmonary tuberculosis, as it was not found in any case in combination with positive sputum.

5. Parenchymal infiltration, on the other hand, as seen by the Roentgen ray, is of great importance, for 68 per cent had positive sputum.

6. In a certain percentage of cases, the Roentgen ray will show a lesion not demonstrated by physical signs, as proved by the above comparisons, there being 11 per cent of cases with involvement of the second apex not shown by physical signs.

7. The Roentgen ray more often presents a greater involvement (35 per cent) than is shown by physical signs (5 per cent).

8. A parenchymal Roentgen ray lesion and rales usually occur together, this combination taking place in 93 per cent of the above

series, while peribronchial infiltration and rales are almost never found in combination, occurring in 1.6 per cent of cases.

9. Serial roentgenograms, taken from two- to six-month intervals, portray before our eyes the ever changing pathology of the lungs of the tuberculous, thus giving us an insight as to the progress and prognosis, which can be obtained in no other way.

10. The time is at hand when the clinician must be trained (as Dunham expresses it) in the "roentgenoscopic pathology of the lungs." It is just as important that he make his own Roentgen ray interpretations as it is that he make his own physical examinations.

11. If we are to make the Roentgen ray of real value, we must discard the idea that peribronchial thickening, when it reaches the periphery, and infiltration of the hilum have any significance in the diagnosis of pulmonary tuberculosis. Clinicians and roentgenologists, who still believe in this theory, are causing much confusion and misunderstanding and have brought great disrepute on the true value of the Roentgen ray.

12. It is urgently important that all staffs of tuberculosis hospitals adopt a uniform, pathologic-anatomic classification that can be used conjointly by the clinician roentgenologist and pathologist.

13. On account of the great value of the Roentgen ray, it is of doubtful expediency for tuberculosis sanatoria to limit the use of Roentgen ray films. Their more extensive use should be encouraged, for the greater efficiency attained would save the extra expense many times over.

14. If we are to progress in the knowledge of tuberculosis, it is imperative that every effort be put forth to obtain permission to perform more necropsies. To increase our proficiency, we must not only compare the actual lesions with the roentgenoscopic picture and physical findings; but we must know, by actual study, the ever changing pathologic picture which is so essential to a thorough knowledge of tuberculosis.

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DIABETIC CHILDREN'S DIETS IN DIFFERENT CLINICS.

Based on 532 Reports.

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The great courtesy of a number of the most careful students of diabetes in furnishing details on their patients, with a smaller amount of like discharge data found in print, made possible this survey of diets fed to children with diabetes. Body weights, especially in children, vary so widely as to make difficult any rapid mental comparison of diets stated in the current fashion in absolute units, that is, grams per twenty-four hours. If these, however, be prorated to the body weight in grams per kilogram, the distinctions between diets become far clearer. For normal children, Holt and Fales[1] published such tabulations, which served as a stimulus toward application of the same method to diabetics.[2] The present extension of the study was encouraged by finding that the method had been independently used by Mason[3] and by Wilder,[4] and also by Corson-White's generalization:[5] "Varied studies on nutrition have shown that the chemical requirements of a diet are in their ultimate analysis essentially the same for all species of the higher animals—that is, all require approximately the same amount of protein, fat, carbohydrate, and so on, per kilo of body weight, while the morphology of the tract decides the physical properties of the diet."

The present design has been first to ascertain the average juvenile diabetic's diet, and to contrast this with the normal. Second, from the reports of each investigator an average has been made, and the difference between that average and the grand average for all the investigators has been examined by biometric technique to determine whether the difference be significant. Those differences which are found to be significant are in part incidental to the planning of a diet approximating a patient's habits and wishes, in the effort to arrange a régime to which he will be likely to adhere; but in part are no doubt intentional. What these intentions seem to be is indicated by the tables. Whether tendencies away from the average diabetic diet (maybe toward the normal diet, maybe away from it) be wise (in general, that is, since particular patients naturally need personal modifications) must be left to demonstration by end results, such as length of life, achievement of growth in height, weight, activity and general vigor.

The raw data, deriving from the insulin period, necessarily are the expression of changing views and, therefore, patently must not be assumed to represent anybody's precise practice at this moment.

None the less, they are believed to be more comprehensive than any yet published and to afford accordingly the most accurate evidence of actual practices (as distinct from principles) which is available today to guide those of us with less experience.

The material sought has been limited to patients not yet twenty years old, because the raising of children is perhaps the toughest problem in diabetes. There were 282 such cases. Since months in the life of a child are accompanied by changes greater than years in the life of an adult, since a diabetic child on subsequent discharges from observation ordinarily shows variations in status as great as those between individuals, and since statistics are enhanced by size, it has seemed legitimate here to tabulate not cases but data obtained on discharge. There were 532 such reports. Even thus the series is too small to be grouped by years of age, as would be better, and is classified only according to first and second decades of life. Let us now analyze in turn the average diet, the calories per kilo, protein per kilo, the division of the remainder of the food between carbohydrate and fat, and finally the insulin requirement.

Diabetic versus Normal Diet. The differences between normal and diabetic diets are well known in general, but are worth demonstration in figures (Table I), largely as a basis of comparison for future tabulations. The diabetic's lower calories, lower protein, lower carbohydrate are manifest, but the deficits compared with normal are happily somewhat less striking than was noted in my previous reports.

TABLE I.—DIABETIC VERSUS NORMAL AVERAGE DIET.

	Insulin units (24 hours).	C/k.	P/k.	F/k.	Cal/k.	FA/k.	G/k.	FA/G.
Decade I. Normal . .	0	10.7	3.2	3.4	86	4.6	12.9	0.36
Decade I. Diabetic . .	21	3.8	2.7	5.0	71	5.7	5.9	1.0
Decade II. Normal . .	0	7.5	2.2	2.3	60	3.1	9.0	0.3
Decade II. Diabetic . .	40	2.1	1.6	3.5	46	3.8	3.4	1.1
Decades I and II. Diabetic	33	2.7	2.0	4.0	55	4.5	4.3	1.0

C/k = grams carbohydrate eaten in twenty-four hours divided by patient's body weight in kilograms.

P/k = grams protein eaten in twenty-four hours divided by patient's body weight in kilograms.

F/k = grams fat eaten in twenty-four hours divided by patient's body weight in kilograms.

Cal/k = number of calories eaten in twenty-four hours divided by patient's body weight in kilograms.

FA (fatty acids) = 0.46 P + 0.9 F.

G (glucose) = C + 0.58 P + 0.1 F.

FA/G—if over 1.5 will produce acidosis (Woodyatt).

Statistical Arithmetic. "None of you will contradict me," said Lawrason Brown,[6] "when I say that statistics are very dry, but

some of you may dispute me when I say that only by statistics does the world, lay or medical, advance." Whipple,[7] too, in his little manual on Vital Statistics remarked sympathetically: "Many of you have forgotten most of your arithmetic . . . dread the new methods founded on accurate statistical studies. There is no need of this fear." Emboldened, though mindful of pitfalls, I have tried to use the simpler methods of the biometricians. Pearl's book on medical biometry[8] is invaluable. Harris and Benedict[9] have skillfully compressed the subject into about a dozen pages. Although briefer definition may be rash, it will be attempted here for the benefit of those unacquainted with statistical methods.

N = the number of observations in a given series, say from a certain clinic.

M = the arithmetic mean or ordinary average.

S. D. = the standard deviation, which is preferred by statisticians to the average deviation, as a criterion of the variation (scatter, dispersal) of the individual measurements around the average. The S. D. is calculated by noting the deviation of each measurement from the average, then squaring each deviation, adding these squares, dividing by the number of measurements (N), and extracting the square root of the quotient. The resulting S. D. tells us the variation in *absolute* units, such as calories. Obviously a variation, of say 10 calories, is much less significant if the average happens to be 100 calories than if it be 1000 calories. Hence, quite naturally, we transmute our S. D. into a percentage, by dividing it by the average.

C. V. = then the coefficient of variation, that is, percentage or relative variation = 100 S. D./M.

E = the probable error. This term is agreed to be unsatisfactory but is hallowed by use. It does not refer to possible inaccuracies of the observations on the patients; these are assumed to have been reduced to the minimum by preliminary planning of appropriate technique and its careful execution. The term does refer to "probable errors of random sampling." That is, a "sample" (series of observations) taken at "random" (for instance, on consecutive patients in a given clinic) will yield an average which will usually differ to some extent from the average derived from a second sample. This difference is often so small as to appear to ordinary inspection of doubtful significance, but nevertheless may be definitely significant when compared with its probable error (probable error of the difference = $E_{Diff.}$). This comparison is done by dividing the difference by its probable error (Diff./$E_{Diff.}$); if the quotient amounts to 3 the odds are 22 to 1 that the difference is significant, while if the quotient comes out more than 3 the odds are even greater in favor of its significance.

E = the probable error of each given average (M) and = 0.6745 S. D./N, the reckoning being easily performed by use of Pearson's tables.[10]

$E_{Diff.}$ = the probable error of the difference between two averages, and is secured by squaring the probable error of the first average and the probable error of the second average, adding the two squares, finally extracting the square root.

For example, in Table II, the average number of calories taken by Woodyatt's patients was 79.3 ± 2.20 (M ± E), while the grand average for all the patients was 71.7 ± 0.80 calories. The question is whether the difference is significant or merely a result of chance.

The calculation:

$$\begin{array}{rrrrrrrr} & \text{Difference} & = & 79.3 & - & 71.7 & = & 7.6 \\ (2.20)^2 & + \ (0.80)^2 & = & 4.84 & + & 0.64 & = & 5.48 \\ & \sqrt{5.48} & = & 2.341 & & & & \\ & \text{Difference} & = & 7.6 & \pm & 2.341 & & \end{array}$$

Thus the difference is 3.2 times its probable error; and we may recollect that it has been customary among biometric workers to consider a difference three or more times its probable error as almost certainly significant.

Calories per Kilo. Turning now to distinctions between diabetic clinics, and first to the calories, we find in Tables II and III facts too detailed for full discussion at this time, but put on record in the belief that they may be of value for reference in future tabulations.

Notable is the great variability (measured by the coefficient of variation) in calories fed by any given observer to his several patients; the grand average variability for all the observers amounts for the first decade to 22 per cent, and to 28 per cent for the second. Even in the face of these large variations, the smallish difference between the average for any observer and the grand average may be significant, when compared with the probable error of that difference (Diff./$E_{Diff.}$). Now this quotient has been calculated out (last column in Tables II and III, except when inspection alone sufficed to tell that the quotient would be too small to signify). Note the quotients of 3 or more. These warrant the statement that calories significantly *lower* than the average have been fed in both Decade I and II by Joslin, while *high* calories have been fed in Decade I by Woodyatt, Allen and Mosenthal, in Decade II by none of these but by Boyd and Hartmann. It is curious to find in some clinics high diets fed to Decade I but not to Decade II, and *vice versa* in others. It is, therefore, intensely interesting to speculate whether a future tabulation would show more consistent tendencies; this should be the case if the law noted by Corson-White for normals be applicable to diabetics and be applied. This seems most likely to prove true for patients whose insulin deficit is moderate, less likely for patients whose insulin need is very large.

TABLE II.—CALORIES PER KILO IN DECADE I.

Observer.	Number of cases.	Number of reports. N.	Mean. M.	Probable error. ±E.	Standard deviation. S. D.	Coefficient of variation. C. V.	Diff. E Diff.
Woodyatt	11	14	79.3	±2.20	12.2	15.4	3.2
Boyd	4	15	78.4	±2.62	15.0	19.2	2.4
Allen	20	20	76.5	±1.74	11.5	15.1	3.0
Mosenthal	3	3	75.3	±0.66	1.7	2.3	3.5
Hartmann	8	8	73.8	±2.90	12.2	16.5	0.7
Geyelin	12	44	73.2	±2.06	20.3	27.8	
Smith	13	13	73.1	±3.23	17.3	23.6	
Other clinics	9	9	71.1	±3.09	13.7	19.3	
Sansum	12	23	70.9	±1.94	13.8	19.5	
Joslin	33	38	61.3	±1.18	10.8	17.7	7.3
Grand average	125	186	71.7	±0.80	16.1	22.4	

TABLE III.—CALORIES PER KILO FOR DECADE II.

Observer.	Number of cases.	Number of reports. N.	Mean. M.	Probable error. ±E.	Standard deviation. S. D.	Coefficient of variation. C. V.	Diff. E Diff.
Boyd	5	7	65.7	±3.31	12.9	19.6	5.7
Hartmann	10	12	59.9	±1.59	8.2	13.7	8.0
Geyelin	13	92	49.3	±1.06	15.2	30.8	2.3
Sansum	24	43	48.6	±1.10	10.7	22.0	1.2
Woodyatt	34	56	47.7	±1.06	11.8	24.7	
Allen	15	15	46.7	±1.64	9.4	20.1	
Other clinics	13	13	46.4	±2.46	12.3	26.5	
Mason	17	42	43.8	±1.26	12.1	27.7	2.1
Joslin	43	66	37.3	±0.64	7.7	20.6	11.5
Grand average	157	346	46.6	±0.49	13.4	28.8	

Actual, not normal, body weights have been used in this paper, primarily because normal weights could not be properly estimated without knowledge of the children's heights, and these had not been recorded in many instances. Secondly, even when the height and age be known, the normal weight for a particular child is not always easy to state precisely, owing to differences between tables of "standards;" difficulties inherent in the frequent impossibility of learning racial and familial inheritance of build. In the next place, even when a normal weight be established with reasonable precision, the question yet remains open as to whether a normal average weight is really ideal for a diabetic child or whether such children do better in the long run if they are fed toward a lean build, say ten per cent under the average for their sex, stock, age and height.

Protein per Kilo. The variability of the protein allowance (Tables IV and V) was even more marked than was true of the calories; the average coefficient for the first decade was 31 per cent, and 34 per cent for the second. Significantly low-protein diets were used in both decades by Joslin, in Decade I by Mosenthal and perhaps Smith, and in Decade II by Mason and perhaps Woodyatt. High protein was used in Decade I by Allen, and in Decade II by Geyelin and Hartmann.

TABLE IV.—PROTEIN PER KILO IN DECADE I.

Observer.	Mean M.	Probable error. ±E.	Standard deviation. S. D.	Coefficient of variation. C. V.	Diff. E Diff.
Allen	3.34	±0.121	0.80	23.9	4.4
Geyelin	2.94	±0.075	0.73	24.8	2.0
Sansum	2.83	±0.107	0.76	26.8	0.5
Hartmann	2.74	±0.211	0.89	32.3	
Woodyatt	2.69	±0.067	0.37	13.8	1.0
Boyd	2.67	±0.187	1.07	40.6	0.1
Other clinics	2.57	±0.309	1.38	53.5	0.6
Mosenthal	2.50	±0.032	0.08	3.4	5.2
Smith	2.34	±0.162	0.87	37.1	2.6
Joslin	2.30	±0.041	0.37	16.2	8.1
Grand average	2.77	±0.042	0.85	30.8	

TABLE V.—PROTEIN PER KILO IN DECADE II.

Observer.	Mean M.	Probable error. ±E.	Standard deviation. S. D.	Coefficient of variation. C. V.	Diff. E Diff.
Geyelin	2.08	±0.056	0.798	38.3	6.3
Hartmann	1.91	±0.055	0.281	14.7	4.0
Allen	1.86	±0.076	0.437	23.4	2.0
Boyd	1.84	±0.145	0.570	30.9	1.0
Sansum	1.63	±0.037	0.361	22.1	
Woodyatt	1.60	±0.033	0.365	22.8	2.6
Mason	1.51	±0.040	0.380	25.2	4.2
Other clinics	1.43	±0.107	0.529	36.9	2.5
Joslin	1.39	±0.023	0.278	20.0	10.0
Grand average	1.70	±0.021	0.580	34.1	

Carbohydrate Fat Ratio. Now that the amounts of calories and protein have been examined, there remains to be determined the division of the rest of the diet between carbohydrate and fat. The more painstakingly one figures (successive columns in Tables VI and VII) the smaller is the difference between the average practice in different clinics. That is, the differences are striking in terms of carbohydrate per kilo, less striking in terms of glucose per kilo,

and relatively small on the whole in terms of the fatty-acid : glucose ratio. This ratio has since the advent of insulin tended to fall, and in the present study is found to be down to 1.0 in Decade I for Geyelin, Joslin, Sansum and Bertnard Smith, and in Decade II for the first three named. Although this FA:G ratio affords probably the most accurate index number to express the relative amounts of available glucose and fat in the diet, it entails considerable labor, and in view of the similar order in the three columns in Table VI further analysis here of the tendency toward high-carbohydrate diets will be continued in the simpler terms of carbohydrate per kilo.

TABLE VI.—CARBOHYDRATE AND FAT PROPORTION, DECADE I.

LOWEST FAT RATIO GIVEN FIRST.

	C/k.	G/k.	FA/G.
Sansum	5.0	7.0	0.8
Geyelin	4.7	6.9	0.8
Joslin	3.2	4.9	1.0
Smith	4.1	6.0	1.0
Woodyatt	3.7	5.9	1.1
Allen	3.5	6.0	1.1
Mosenthal	3.5	5.5	1.1
Boyd	2.9	5.1	1.4
Other clinics	3.2	5.3	1.5
Hartmann	2.1	4.3	1.6
Grand average	3.8	5.9	1.0

TABLE VII.—CARBOHYDRATE AND FAT PROPORTION, DECADE II.

	C/k.	G/k.	FA/G.
Sansum	2.7	4.0	1.0
Geyelin	2.6	4.1	1.0
Joslin	1.8	2.9	1.0
Smith	4.4	6.5	1.2
Other clinics	1.9	3.1	1.2
Mosenthal	1.8	2.9	1.2
Woodyatt	1.8	3.1	1.3
Allen	1.6	3.1	1.4
Mason	1.4	2.7	1.4
Boyd	2.4	3.9	1.5
Hartmann	1.5	3.1	1.8
Grand average	2.1	3.4	1.1

High Carbohydrate. By this is meant *continuous* high carbohydrate, not temporary meal or cereal cures. A table plotted for the frequency of each carbohydrate per kilo allowance, running all the way from 0.5 to 11.1 gm. C/k, was so unwieldy that it is better summarized. The average was 2.9 g/k, the median 2.3, and the value at or above which lay: 20 per cent of all the observations, was 3.9 g/k; 15 per cent was 4.4 g/k; 10 per cent was 5.1 g/k; 5 per cent was 6.2 g/k.

The 10 per cent group contains scattering observations from Allen, Joslin, Woodyatt and others, but most of the reports in this group, and nearly all in the 5 per cent group, come from Geyelin or from Sansum. Whether these high-carbohydrate diets have come to stay, whether for many or few patients, can only be guessed at

present. But a brief analysis of the way they run may be of some interest. If high-carbohydrate diets be defined as those of 4.4 g/k or more, that is, 15 per cent of all the observations, while those below this level be grouped as lower carbohydrate diets, the high *versus* lower, for Geyelin and for Sansum, may be compared by the averages in Table VIII, column FA/G. The high-carbohydrate groups of both observers, in both decades approach Holt-Fales' normal FA:G of 0.3 considerably more closely than do any other groups reported. Of the two Sansum has pushed nearer the normal; at the cost of more insulin, as would be expected.

Insulin. The dosage per twenty-four hours averaged 32 units, ranging roughly from an average of 20 units for Decade I and 40 units for Decade II (Table I); up to 24 units (Geyelin's high-carbohydrate diets) and 44 (Sansum's high) for Decade I, and 50 (Geyelin's high) and 100 (Sansum's high) for Decade II (Table VIII). The maximum was 212 units (Sansum's patient No. 7689, a boy aged eighteen years and five months, weighing 67.6 k, on a diet of carbohydrate, 300; protein, 116; fat, 150; calories, 3000).

TABLE VIII.—HIGH VERSUS LOWER CARBOHYDRATE DIETS.

	Insulin (24 hrs.).	C/k.	P/k.	F/k.	Cal/k.	FA/k.	G/k.	FA/G.
Decade I:								
High, Sansum	44	7.2	3.2	3.8	76	4.9	9.5	0.5
High, Geyelin	24	6.4	3.2	5.0	84	6.0	8.8	0.7
Lower, Geyelin	17	2.7	2.6	4.5	62	5.2	4.6	1.1
Lower, Sansum	24	2.2	2.3	5.2	65	5.8	4.0	1.4
Decade II:								
High, Sansum	103	5.1	2.0	2.5	51	3.1	6.5	0.5
High, Geyelin	50	5.0	2.3	3.8	64	4.5	6.7	0.7
Lower, Geyelin	52	2.2	2.1	3.3	46	4.0	3.7	1.1
Lower, Sansum	64	2.2	1.6	3.7	48	4.0	3.5	1.1

If each observation of insulin be tabulated referred to each kilogram of body weight, from 8 to 75 k., the result is so diffuse that it is better consolidated into 5 kg. groups (Table IX). The lighter weight children used more insulin per kilo. The grand average was 1.0 unit per kilo.

TABLE IX.—INSULIN IN RELATION TO BODY WEIGHT.

Weight in k.	Insulin per k.	Weight in k.	Insulin per k.
*10	1.6	50	0.8
15	1.3	55	0.9
20	1.0	60	0.9
25	0.9	65	0.3
30	1.0	70	1.4
35	1.0	75	1.0
40	0.9	Average all groups	1.0
45	1.0		

* The group 10k. includes weights from 7.5 to 12.4k., the group 15k. from 12.5 and under 17.5k., and so forth.

As carbohydrate increased (Table X) the insulin usage decreased, up to about 150 gm. carbohydrate, whereas higher carbohydrate diets demanded rather more insulin per gram of carbohydrate.

TABLE X.—INSULIN IN RELATION TO CARBOHYDRATE.

Carbohydrate grams (24 hours).	Insulin units (24 hours).		Insulin units per gm. carbohydrate.	
20–9	19		0.76	
30–9	21		0.60	
40–9	21		0.47	
50–9	24		0.44	
60–9	25		0.38	
70–9	31	Or grouped, average 28	0.41	or 0.37
80–9	27		0.32	
90–9	30		0.32	
100–9	24		0.23	
110–9	22		0.19	
120–9	32	or 25	0.26	or 0.20
130–9	25		0.19	
140–9	19		0.13	
150–199	41		0.23	
200–249	73		0.32	
250–299	70		0.25	
300–349	95		0.29	

Summary. The expression of diets in calories per kilo and grams per kilo body weight is believed to reveal more precisely than is now known the diet distributions actually prescribed in the years since insulin became available, and likewise to clarify such trends as diverge sufficiently from the average to demand discussion.

Current practice, as seen in 532 reports from different clinics, is tabulated in a variety of ways.

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CHRONIC LIGNEOUS THYROIDITIS (RIEDEL'S STRUMA).

Five Case Reports with Pathologic Notes.

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A lesion of the thyroid, which is of sufficient rarity to make the occasional cases which occur worth reporting, is known by various terms, most commonly as "chronic ligneous thyroiditis or Riedel's struma." This was first described as a clinical and pathologic entity by Riedel[1,2,3] in 1896 and since that time apparently only 35 cases have been reported in the literature by fifteen authors. Accordingly it seemed as if the 5 cases seen during the past year at the Lahey Clinic in Boston should be recorded.

Clinical Symptomatology. The disease occurs in both males and females, but there is a marked preponderance in women. All 5 of our cases were found in women and in the 35 reported cases only 10 occurred in males, so that the ratio seems to be about 3 to 1. The age incidence offers less constant findings, but the condition tends to occur in the fourth decade on, although a number of cases are reported in the second and third decades, the youngest being in a woman, aged twenty-three years. Riedel mentions a probable case in a child, aged four years, but no detail is given.

The symptoms are those of actual pressure or constriction of the trachea, esophagus and recurrent laryngeal nerves. In the earlier stages this may exist simply as a fairly constant sensation of "fullness" in the throat. In the more advanced cases *dyspnea* is the most frequent symptom, its degree varying directly with the tracheal pressure. *Dysphagia* may occur, although its presence is unusual. In many of the recorded cases it was absent, and Bohan makes the absence of dysphagia a point in differential diagnosis. *Aphonia* may occur, but is also relatively infrequent. We have seen it temporarily present in 1 case.

A well-marked goiter is usually present in typical cases of ligneous thyroiditis. The increase in size of the gland is usually very slow and goes unnoted until attention is called to the mass by accident. As a rule there is very little noticeable change in the size of the goiter over a period of many months. The lesion is usually not tender and does not cause pain.

The swelling may be unilateral, but it is more commonly bilateral

and symmetrical. On palpation the extreme density of the gland is the most noticeable feature. There is a loss of the normal elasticity usually felt in the thyroid, and instead it has a feeling of extreme hardness. On palpation the surface of the gland may feel smooth or but slightly irregular in the typical case. In other cases distinct nodules may be present, and thus make the clinical resemblance to a multiple colloid adenomatous goiter quite marked. The regional lymph nodes are not enlarged in typical cases, and when they are, may lead to confusion in the differential diagnosis.

Perhaps the most important point in the examination of the gland after the presence of its stony hard nature is noted, is its adherence to the surrounding structures in the neck. In other types of goiter the outlines of the thyroid can be clearly palpated and mapped out. In Riedel's struma, the borders of the gland cannot be distinctly distinguished because of the adhesions extending from the gland to the vessels, muscles and fascia of the neck. In this respect, as in its unusual hardness, it resembles carcinoma, but carcinoma of the thyroid, which has extended into the various structures of the neck, also is found to have extended to the skin, which is usually edematous and adherent. In Riedel's struma, however, the skin has been involved in but one of the reported cases, and not at all in this series of ours.

Another point of value in differential diagnosis is the absence of true toxic symptoms as evidenced by a normal basal metabolism, preoperatively. And, conversely, no clinical evidence of myxedema was present in any case before operation. Certain symptoms are present sometimes in these cases which in the presence of a goiter, may well mislead the clinician into making a diagnosis of toxicity before the basal metabolic rate is known. These are tremor and nervousness. Loss of weight also occurs and at times may be quite marked, but basal-metabolism studies will rule out the presence of toxicity in these patients and the proper diagnosis may then be suspected from the typically "iron hard" feeling of the gland.

No fever is present, as a rule, in typical cases of Riedel's struma. A slight elevation of the white blood count may be present.

Treatment. Surgery apparently offers the only permanent relief. A subtotal thyroidectomy should be done on the lobe or lobes involved. Three subtotal thyroidectomies were performed in our series with complete relief of pressure symptoms. In 1 case a subtotal hemithyroidectomy was performed when the process involved but one lobe of the gland. Clinical relief followed this procedure. In 1 case sections for pathologic diagnosis only were removed from each lobe. This patient still has a palpable goiter and is not relieved of her chief complaint, a sense of pressure and fullness in the neck. She doubtless will require a thyroidectomy at a later date.

In this series of 5 cases of Riedel's struma, 4 had an appreciable

FIG. 1.—Camera lucida drawing—Zeiss 1.7 obj., No. 4 ocular. Case V. Illustrates the diffuse infiltration of the interstitial stroma by mononuclear cells, chiefly of the lymphoid series, with the gradual replacement of the thyroid acini. The persistent hyperplasia of the acinar epithelium is well brought out, with many large acidophilic staining cells which in places almost appear syncytial in arrangement.

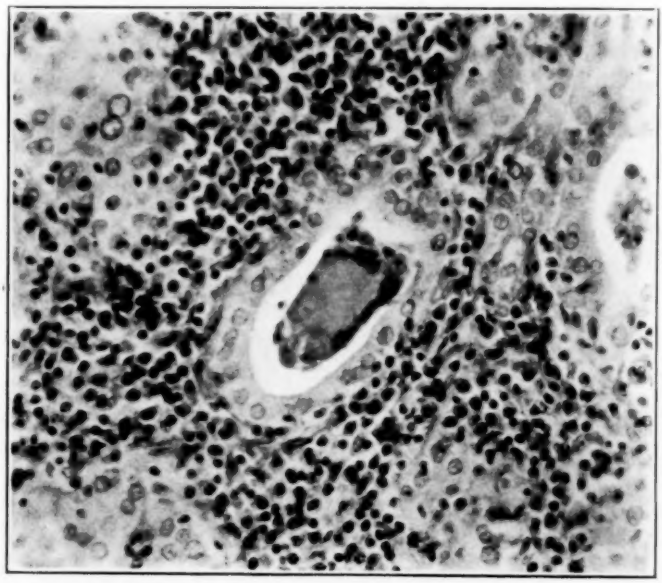

FIG. 2.—Photomicrograph—high power—Leitz obj. 4 mm., ocular No. 2. Same Case V. Illustrates the catarrhal desquamation of the acinar epithelium into the lumen of the alveoli, and the formation of a "pseudogiant-cell." The extraordinary resistance to atrophy of the alveoli is to be especially noted.

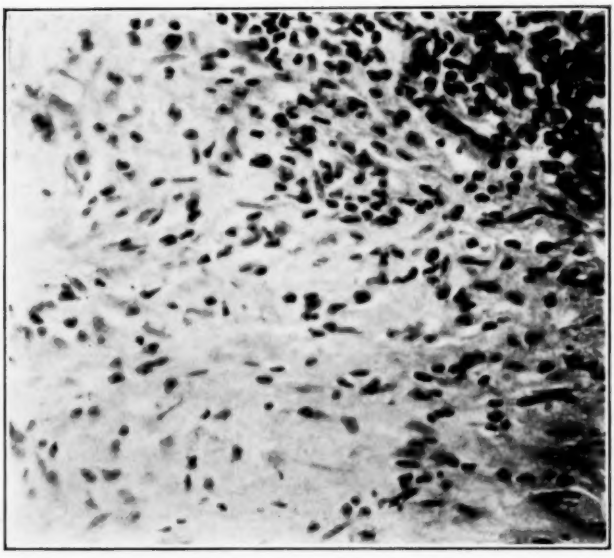

FIG. 3.—Photomicrograph—high power—Leitz obj., 4 mm., ocular No. 2. Case IV. Illustrates the late lesion with replacement of the acini by fibrous tissue, still containing islands of lymphocytes.

amount of thyroid tissue removed at operation but the fifth had merely small sections removed from each lobe for diagnosis. Of the 4 patients on whom a partial thyroidectomy was done, 3 have been followed postoperatively. All 3 have evidence of myxedema both by basal metabolic tests and by clinical examination. Two are receiving thyroid medication with marked improvement of symptoms. The patient from whom only sections were taken for diagnosis has not as yet developed myxedema.

Cases of myxedema following thyroidectomy in Riedel's struma have been reported. Unquestionably patients having this disease must be followed for may months after operation with this possibility in mind. It is our belief that partial thyroidectomy in Riedel's struma will be followed by myxedema in a very large proportion of cases.

Several cases have been reported in the literature that have been treated by Roentgen ray alone, but they have been followed by recurrence or persistence of the original difficulty. Ewing[4] believes that the most successful treatment consists of partial thyroidectomy, followed by radiation when the entire gland is involved.

It is of interest to note that the voice weakness and occasional aphonia noted before operation in one of our cases was lost after the removal of the pressure of the enlarged thyroid gland.

The following case reports are given in abstract form together with a copy of the pathologic reports:

Case Reports. CASE I.—(N. E. D. H. No. 32145.) Mrs. H. M., aged forty-nine years, has always lived in Maine. Her family history is negative.

Past History. She has had nine pregnancies, with one miscarriage, had diphtheria and the other usual children's diseases, and one attack of rheumatic fever (?) six years ago. The menstrual history has been normal; the last period was six months ago. This apparently marked the menopause. Her weight has ranged from 168 to 164 pounds during the past two years.

Present Illness. She was admitted to the hospital because of a palpable mass in her neck, which has existed for the past nine months and has varied considerably in size. At one time it was somewhat sore. She also complains of a small lump on the left ankle, which has been slowly increasing in size for the past few months.

Physical Examination. She is a fairly well-developed and nourished woman. There seems to be some slight dyspnea on exertion. There are no physical findings to suggest a hyperplastic type of goiter. There is a nodular hard mass, rather fixed in character, involving the right lobe particularly, but extending to the isthmus. This apparently produces some pressure in the neck. The cervical lymph nodes are unquestionably enlarged. There is no exoph-

thalmos. The blood pressure is: Systolic, 200; diastolic, 102. There is some edema of the extremities. The basal-metabolic rate is +9. Pulse rate from 60 to 70.

Roentgen Ray Findings. The chest is negative. There is no displacement of the trachea. There is no evidence of substernal thyroid. Laryngoscopic examination negative. A preoperative diagnosis of carcinoma of the thyroid or chronic thyroiditis was made. Repeated urine examinations showed a very slight trace of albumin, which disappeared with a reduction of the specific gravity from 1026 to 1008. There was a slight trace of sugar; the blood findings showed a red count of 6,000,000, a white count of 11,350. The hemoglobin was 90 per cent, and a differential count showed 53 per cent polymorphonuclears, 31 per cent lymphocytes, and 16 per cent large mononuclears.

Operation. Ethylene anesthesia. The thyroid gland was exposed in the usual manner. The right lobe was very hard and somewhat nodular. It was adherent to the jugular vein. Sections were removed from both lobes for histologic examination. Discharged one week following operation in satisfactory condition with some relief of symptoms.

Basal metabolism six days after operation was +10, the pulse rate 70 to 80. A further examination was made two months after operation, at which time the metabolism was +3 and the pulse rate 60 to 64. The patient's general condition was quite satisfactory. The right side of her neck still shows a firm stony hard mass firmly fixed to the surrounding tissues. She complains of no difficulty in swallowing or breathing, but still has some sense of fullness in the neck.

Pathologic Report. (DS-25-1603.) *Microscopic.* There is an extraordinary diffuse infiltration and replacement of the normal thyroid tissue by lymphocytes, in many places producing complete atrophy of the acini. Here and there abortive attempts at glandular hyperplasia are noted. There is no evidence of malignant change in the epithelium. There are many lymphoid follicles. It represents a relatively early case of Riedel's struma.

CASE II.—(N. E. D. H. No. 30305.) Mrs. C. W., aged sixty-seven years.

Family History. A sister had a swelling of her neck at about the age of eleven years, which persisted only for a short time.

Past History. She had the usual children's diseases, but otherwise has been in almost perfect health until about two years ago. At puberty, however, she noted a swelling in her neck similar to that of her sister. This disappeared after a few weeks. About two years ago she began having symptoms referable to her heart, with palpitation, a rapid rate, and a high blood pressure. She developed dyspnea and became sensitive to low temperatures.

For the past two weeks she has felt listless and disinclined to do her usual housework. She thinks she has lost weight during this interval. She has had no treatment except for her high blood pressure. Her weight until the present time has remained fairly constant. She sleeps fairly well; is easily fatigued.

Physical Examination. Is essentially negative except for the presence of marked enlargement of the thyroid gland, involving both lobes and the isthmus, the left lobe being somewhat larger than the right. There is moderate pulsation, which is transmitted. By Roentgen ray examination the goiter is found to have extended substernally, with deviation of the trachea to the right. This is accompanied by dilatation of the thoracic veins. There is no enlargement of the cervical glands, but a rather marked tremor of the hands and feet.

Laboratory Data. Urinary examinations have shown a persistent slight trace of albumin and occasional hyaline casts. The Wassermann test was negative. Blood sugar, 90; nonprotein nitrogen, 28. The blood examination showed a normal red count of 4,720,000; the white count, 6950; hemoglobin, 85 per cent; Differential count: Polymorphonuclears, 74 per cent; lymphocytes, 15 per cent; large mononuclears, 7 per cent; eosinophiles, 3 per cent. Clinical diagnosis of multiple colloid adenomatous goiter was made.

Operation on June 4 revealed a moderately large multiple colloid adenomatous goiter which was removed by subtotal thyroidectomy. The patient had a systolic blood pressure of 300 during the operation, but appeared in good condition at its conclusion.

Subsequent Notes. June 10: Recovery from operation was marked by several days of semiconsciousness, merging to unconsciousness. Her general condition was very poor. June 16: During the past few days the patient has developed a left hemiplegia with speech involvement. June 21: There is considerable improvement in general condition. She can now move her arm and leg and her speech is improved. June 29: The patient is discharged, showing marked improvement. Some slight drainage from the neck wound and the speech is still somewhat thick.

Basal metabolism before operation was +24 on one day and +10 on another. The pulse rate ranged between 80 and 90 at the first test and 70 and 76 at the second test.

She was readmitted August 25 for examination two months after operation. At this time her general condition was much improved. She had scarcely any evidence of hemiplegia and no clinical evidence of myxedema. Her basal rate was −8 with a pulse rate of 70 to 80. Report from this patient's home physician ten months after operation is that she feels much improved since he gave her small daily doses of thyroid extract. Her blood pressure is now 250 systolic and 140 diastolic. No recent metabolism test has been done.

Pathological Report. (DS-25-817.) *Microscopic.* The sections microscopically present a fairly characteristic picture of Riedel's struma with lymphocytic replacement of the normal thyroid tissue. There is very diffuse interacinar lymphocytic infiltration with actual resulting atrophy of the alveoli. In some areas a compensatory proliferation of the epithelium is noted. The colloid is reduced to a negligible amount. There are several definite lymphoid follicles noted. No mitoses are seen. Under low power the picture suggests a lymphoid tumor invading the thyroid. Beginning fibrosis is seen in some areas. The sections also include a small simple adenoma of the fetal type.

Diagnosis. Fetal adenoma. Riedel's struma.

CASE III.—Mrs. J. C., aged forty-nine years, has been married twenty-two years. She has always lived in Boston. Her family history is negative.

Past History. Her general health has been good. She has had one normal pregnancy. There is no infectious history except of tonsillitis.

Present Illness. Began as a swelling of the neck for the past three or four months, with some sense of pressure with certain positions of the head. She had been taking potassium iodid for some time under medical supervision. Her last period was six months ago and apparently represents the menopause. Her weight has been constant. There is some palpitation of the heart on exertion, and hot and cold flashes. Has had constant sense of constriction in the neck with an irritating cough. There is intermittent hoarseness. She has been more nervous and irritable than normal and slept poorly, fatiguing very easily lately. The thyroid is definitely enlarged, rather symmetrically. It appears free. There is no obvious deviation of the trachea. There is some pigmentation of the eyelids and body generally, particularly in the folds. The heart rate is 88 and is regular. Laboratory study was essentially negative. The metabolism rate on July 9 was − 9. July 10: A left subtotal thyroidectomy was done, including the removal of the isthmus. The left lobe appeared about twice the normal size, extremely firm in consistency, suggesting malignancy. August 10: The wound healed but somewhat adherent to the underlying muscles.

Examination six months after operation showed no further evidence of thyroid enlargement. The hacking cough and sense of constriction in the neck had disappeared. There was no difficulty in swallowing. The basal metabolism was − 15 with a pulse rate of 64. There had been no gain in weight. Clinically, aside from brittle nails and dry hands, she showed no evidence of myxedema and seemed in excellent health.

Pathologic Report. (DS-25-1054.) *Microscopic.* The sections present a well-advanced stage of the socalled "benign granuloma"

of the thyroid, or Riedel's struma. The tissue under low power is hardly recognizable, being composed of masses of lymphocytes embedded in a dense stroma of connective tissue which creates the impression of atypical lobulation. In these cellular areas occasional acini are found, some few of which contain recognizable colloid. Some of this acinar epithelium has undergone a metaplasia with the formation of large cuboidal cells with greatly increased amounts of cytoplasm which stains intensely with eosin. The lymphoid tissue here and there is reminiscent of follicle formation, but no active follicles can be made out. There is nothing to suggest malignancy.

Diagnosis. Riedel's struma; late stage with fibrosis.

CASE IV.—Mrs. L. B., aged forty-nine years, divorced. Her family history is negative.

Past History. Her general health has been good. She has had two pregnancies. There is no infectious history of significance.

Present Illness. She has had a swelling in the neck, present, she thinks, for several years. Noted first by her doctor whom she consulted for metrorrhagia four months ago. Since that time has been taking iodin and thyroid extract daily. Has had occasional attacks of palpitation and has dyspnea on slight exertion. There is no dysphagia or aphonia. She thinks she has been more nervous than normally, and sleeps poorly. Her chief complaint is in relation to her menorrhagia and metrorrhagia, which has been very profuse for the past two years, her periods lasting two weeks. There has been an increase in weight of 12 pounds during the past year.

Physical Examination. It is essentially negative, except for the local swelling of the neck. There are no eye symptoms. The heart is regular, with a rate of 120. The blood pressure is 200 systolic and 90 diastolic. There is a moderate-sized tumor mass of the right lobe of the thyroid. There is some suggestion of enlargement of the left lobe. On the right this hypertrophy is very firm. The laboratory examinations are negative. The basal metabolism is + 3.

Operation. Under local anesthesia, and ethylene-oxygen gas, a nodular goiter involving the right lobe of the thyroid was exposed, the upper pole of which was retrotracheal. Subtotal thyroidectomy was done, and the pyramidal lobe also was excised. The preoperative clinical diagnosis was multiple colloid adenomatous goiter, with a question of thyroiditis. November 4: Her general condition has been good. Her condition has improved, but there is still some discharge from the wound. Basal metabolism after operation was + 2 with a pulse rate of 84 to 90. Our last examination was made one month after operation. At this time the wound was well healed and there were no evidences of any local difficulty. The general condition was excellent. There was no clinical evidence

of myxedema. A basal-metabolism test could not be done at this time.

Pathologic Report. (DS-25-1625.) *Microscopic.* The sections show a very diffuse lymphoid infiltration of the thyroid. Many areas are found where the thyroid tissue is completely replaced by lymphoid cells which show definite follicle formation. There is some compensatory hyperplasia of the acinar epithelium, with increase in the size of the cells which show more intensive eosin affinity. There is some desquamation and fusion of these cells in the lumina of the alveoli to form pseudogiant cells. The process suggests a moderately advanced stage of the socalled "Riedel's struma."

Diagnosis. Riedel's struma.

CASE V.—Mrs. L. K., aged fifty-two years, has always lived in Massachusetts. Her family history is negative.

Past History. Her general health has been good. She has had seven pregnancies and two miscarriages. She had rheumatic fever (?) twenty-six years ago. There is apparently a history of epilepsy. She has had marked pyelitis, which required frequent cystoscopy because of a stricture of the left ureter. She had a prolapse of the uterus twenty years ago, which was repaired.

Present Illness. For the past six months she has suffered from hoarseness and weakness of her voice. Three months ago she felt a lump on the left side of her throat. She has had weak spells with profuse perspiration. There has been a choking sensation on lying down and fatigue. She has just begun to wear glasses the past two months. She is past her menopause. She complains of pressure in her neck, with dyspnea, some dysphagia and aphonia. She feels more irritable, nervous, and apprehensive than formerly. She is restless and tires easily, but sleeps well. Her weight has been constant for the past four years.

Physical Examination. Is essentially negative except in relation to the thyroid. There is a very slight suggestion of exophthalmos, with pigmentation and edema of the eyelids. The heart rate is 96; the rhythm regular. The systolic blood pressure is 120. There is some slight edema of the legs. There is a definite plum-sized nodule in the left lobe of the thyroid. The skin over it is freely moveable. The metabolic rate, on admission, was + 10.

Operation. On October 17, a subtotal thyroidectomy was done on a very large multiple colloid adenomatous goiter. She was discharged one week later after an excellent postoperative recovery. There had been some hard swelling beneath the skin flap, which was reduced by poulticing.

The basal metabolism on discharge was − 20, the pulse rate ranging from 60 to 84 during the test. At this time there was no clinical evidence of myxedema.

After the patient returned to her home, her physician reported that she had numerous complaints such as a constant sense of being cold, numbness and tingling in the fingers, nervousness and increased fatiguability. She returned to the clinic two months after operation for examination. At this time on three consecutive days her basal rate was − 10, − 5, and − 7. Urine examination was normal, as were also her phenolphthalein excretion and blood nonprotein nitrogen. Her blood sugar and blood calcium were normal. The symptoms of which she complained soon after her operation had disappeared and she felt well. There was no clinical evidence of myxedema. Examination five months later, however, revealed definite evidence of myxedema. Her basal metabolic rate was then − 29. She has been given thyroxin with marked improvement in her general condition.

Pathologic Report. (DS-25-1562.) *Microscopic.* The sections suggest the socalled benign granuloma or Riedel's struma of the thyroid. There is an almost unbelievable lymphoid infiltration of the gland, practically replacing most of the alveoli. Occasional lymphoid follicles are noted. There is beginning fibrosis. The lymphoid element is so prominent and diffusely distributed as to almost raise the question of a tumor. There is nothing to suggest epithelial malignancy, although here and there individual acini are found with hyperplastic large cuboidal cells. Colloid is only rarely seen. Pseudogiant cell formation in the lumina of the persistent follicles is quite prominent as a result of the fusion of desquamated epithelial cells, and the infiltration of lymphocytes.

Diagnosis. Riedel's struma (moderately advanced).

Discussion. The same general observations which Shaw and Smith[5] made are confirmed in these 5 cases. The ages ranged from forty-nine to sixty-seven years. They all occurred in women. Three of them presented a clinical picture suggesting malignancy, while the other 2 were nontoxic in character, but were thought to be of the diffuse adenomatous type of goiter before operation. They all made essentially normal recoveries with relief of their clinical symptoms. None of these cases has been followed for a long enough period of time to be able to give adequate subsequent notes, but at the time of writing they all appeared in good health. It is interesting to note that in a clinic where so many thyroid cases are encountered, so few cases of thyroiditis of any form are seen. I feel that it may be that we have only had our attention called to Riedel's struma to any extent during the past year or two, with the publication of three valuable papers by St. George,[7] by Meeker,[6] and the one cited above by Shaw and Smith. In approximately 1200 thyroidectomies done during the past two years, at the Lahey Clinic, only these 5 cases of chronic ligneous thyroiditis, 1 of tuberculous thyroiditis, and 2 of pyogenic thyroiditis have been

found. Even this number, however, gives a rather higher percentage of cases of Riedel's type than is found in most other reported groups of cases, except the series mentioned by St. George as occurring in the Mayo Clinic, where 48 cases are said to have been seen in the course of 10,500 thyroidectomies. Riedel reported 3 cases in a series of 1064 goiters. Ewing, according to Shaw, has seen 8 cases. Shaw and Smith record 6 cases seen in several years. St. George records 3 cases. Most of the other reports consist principally of single case reports.

Pathology. Grossly, these thyroids are usually recognizable, due to the extreme firmness of their consistency, which has given rise to the various names applied to the condition—"cast-iron struma, woody thyroiditis," and others. The cases in this series varied, 2 of them presenting the extracapsular extension, which Shaw comments upon, but the other 3 were quite well encapsulated and except for the consistency, at first glance did not look unlike the nodular goiter of multiple colloid adenomata. On section these glands are grayish-white in color, with occasionally small yellowish foci representing degenerated centers. They are more or less resilient, and obviously abound in connective tissue intercellular derivatives, particularly collagen. They do not have the usual appearance of malignancy.

Microscopic Findings. Ewing's statement I think has served to clear the confusion existing between the early type of lesion described by Hashimoto[8] and the late lesions which Riedel recorded, and reconcile the fact that these two rather dissimilar histologic pictures merely represent stages in the development of the final lesion. The 5 cases included in this paper present practically a complete gradation of the typical lesion from the early to the late changes. The early lesion consists of a marked lymphocytic infiltration of the stroma. In places this progresses to a point where follicle formation occurs. The germinal centers of these follicles are unusually active, and even occasional mitotic figures can be found.

The acinar tissue in the meantime is undergoing rather constant changes. We find a slow diminution in the size of the acini. The epithelial cells lining them, however, become enlarged, with rather acidophilic staining cytoplasm, such as we see in the metaplasia of malignancy. The nuclei similarly undergo changes, suggesting a cell activity with even rare mitotic figures being found. There is usually, even early in the development of the lesion, a diminution in the colloid content of the acini, such as we see in the hyperplasia associated with clinically toxic thyroid symptoms. There is a second feature, however, which is less frequently observed in the Basedow's syndrome, that of a cellular infiltration into the lumina of the glands, with the formation of structures which under low power resemble rather strikingly granular casts. At the same time

we see a certain amount of desquamation of the lining epithelium, which also tends to produce this granular appearance. Many of these cells fuse, and their nuclei remain apparently viable, so that there is the suggestion of giant-cell formation which has been alluded to by many of the authors. This giant-cell formation I am convinced is simply an inflammatory condition similar to the proliferative hyperplasia which we see in syphilis, tuberculosis and other granulomatous lesions, but is not to be confused with any of them.

This has been brought out by Ewing, who has given the name "benign granuloma" to the lesion. Gradually the cellular infiltration becomes more and more prominent but the outlines of the acini persist for an extraordinarily long time before the cellular infiltration produces actual atrophy and disappearance of the epithelial cells. Slowly connective tissue is seen replacing the glandular structures and in the later stages of the process we find an almost solid mass of connective-scar tissue in which foci of lymphocytes are seen, with occasional acini rather sharply demarcated and reminiscent of the individual mammary glandular structures in the resting state.

These pathologic findings are of extreme interest, as they represent a type of lesion unlike that ordinarily encountered in the other glandular tissues, although Shaw and Smith bring out the analogy of certain inflammatory lesions of the salivary glands. The chief point of interest clinically lies in the establishment of the diagnosis, as the prognosis, as far as we know, is fairly good. Clinically, it is most readily confused with carcinoma, in which the prognosis conversely is exceptionally poor.

Microscopically, the lesion offers certain difficulties of interpretation. Several possible diagnoses are thought of. One of the most likely mistakes is misinterpreting the lesion for a tumor of lymphoid origin. I should be curious to see whether some of the reported cases of lymphosarcoma of the thyroid did not turn out to be, several years later, simply Riedel's struma. Again, the question of absence of thyroid symptoms from the secretory side is difficult of explanation from the histologic side. In the initial stages of the development of the lesion it is obvious that there is a marked glandular hyperplasia, which might readily account for the maintenance of a normal amount of thyroid secretion, but in the later stages of the disease it is extremely difficult to understand how the patient can prevent showing symptoms of myxedema, as there is so very little glandular tissue which persists.

Since preparing this paper, my attention has been called to a classification of goiter by Williamson and Pearse.[11] They offer a rather different conception of this process, and classify these thyroids under the heading of "hyperplastic lymphadenoid (myxedematous) goiter." They define this as a "physiological subnormal gland undergoing compensatory hyperplasia," and claim to have

seen similar pathologic pictures in normal individuals after the age of fifty years. The end result, they suggest, is that seen in established nongoitrous myxedematous cretins. "It is a specific form of atrophy, distinct from the atrophy following Graves' disease, ligation, or Roentgen ray therapy." They dismiss the possibility of such goiters being a granulomatous reaction to a specific infection, but they make one statement which seems to indicate an entirely new conception of the underlying pathology, for they state that the transition from retrogressive lymphadenoid goiter through endothelioma to fibrosarcoma is very probable. Subsequent discussion may serve to clear the confusion which seems to exist in this highly specific type of goiter.

Etiology. Up to the present time no satisfactory explanation for the cause of this condition has been advanced. Syphilis and tuberculosis have been mentioned as possible agents, but can be readily excluded on the basis of histology and lack of corroborative clinical evidence. Poncet and Leriche[9] attempted animal inoculation with spirochetes, without success. Bohan[10] feels that the condition is a simple infectious one, with dental caries or alveolar abscesses as one very probable source of infection, because his case improved following extraction of three teeth. There is the possibility that there may be some relationship to an atypical involution of a hyperplastic gland or even of a parenchymatous colloid goiter, but we have little evidence to support such a hypothesis, although many fields can be found in individual cases of hyperplastic goiter which closely simulate the picture found in Riedel's struma. The chief point of differential interest from the pathologist's point of view lies in whether this condition is a tumor or an inflammatory process. Thus far all the evidence points toward an inflammatory etiology. Meeker presents an interesting hypothesis in suggesting that the source of inflammation may be a simple nasopharyngitis or tracheitis gaining access to the thyroid by a persistent postbranchial body or fetal rest. Her case is the only one in which the presence of this embryologic anomaly has been noted. Having it in mind, careful microscopic search has been made in this series of 5 cases, with negative result. It is true, however, that the material did not in any of the 5 cases represent the entire gland and, furthermore, while many sections were cut from each it is not impossible to have missed such a minute group of cells. It is one of those hypotheses which it is difficult to disprove but which seems to rest on very slender evidence as far as deducing any general conclusions is concerned.

Bacteriology. Cultural attempts were made in one of these cases, with entirely negative results. Material was ground up with salt solution and planted on the usual laboratory media, including hormone agar, blood serum, blood agar, Dorset's egg media, dextrose broth and anërobic media of the Noguchi type for the cultivation

of spirochetes. In none of these was there any growth after as long a period as a month.

Animal Inoculation. Similarly, animal inoculation was attempted with material from this case. A saline emulsion of the tissue was prepared and injected with aseptic operative technique through a small skin incision directly into the thyroid of three rabbits. Two other rabbits were injected similarly with a Berkefeld filtrate of the same material. None of these animals developed the characteristic picture histologically. Those containing the actual emulsified material showed fairly typical areas of acute necrosis and fibrous tissue scarring. No changes were noted in the animals receiving the filtrate alone.

These experiments were made simply with the point in mind of ruling out any specific organism among the more common infectious agents. In this respect they may be considered as satisfactory. Unfortunately no evidence was secured of any value in establishing any less obvious infectious etiologic agent. The condition in this respect might be compared in a limited way to Hodgkin's disease, in which similarly we have the gradual replacement of the lymphoid structures by an unusual type of fibrosis which has been variously interpreted by different pathologists, as being possibly of an infectious nature or of an oncological etiology. In many respects this lesion behaves as a tumor; but the evidence is inadequate to support this hypothesis. Accordingly, we are forced to conclude with the other observers of this disease, that Riedel's struma is a chronic inflammatory lesion of unknown etiology. Whether such cases may proceed to malignancy is a question which only time can answer. This has been brought to our attention recently by 2 additional cases, 1 of which is under considerable doubt as to classification. Here, too, whether the process is developmental or whether it represents a superimposed lesion is very difficult to decide.

Summary and Conclusions. Five cases of Riedel's struma in varying stages of development are presented. A discussion of the clinical and laboratory difficulties of diagnosis is given. Comment on the pathologic lesion, supported by unsatisfactory experimental results, confirm the general opinion that the lesion is one of chronic inflammation of unknown etiology.

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HEMANGIOMA OF THE ESOPHAGUS.

Report of a Case.*

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In approximately 4000 patients complaining of dysphagia examined in the Mayo Clinic benign tumor was found in 3 only. One of the tumors was a myoma, 1 a pedunculated lipoma and 1, in the case reported herewith, a hemangioma.

Report of Case. A man, aged seventy years, was examined February 15, 1926 (Fig. 1). In November, 1925, he had noticed substernal burning. He had coughed and expectorated small amounts of clear mucous secretion continually without progression until three weeks before he came to the Clinic, when he noticed obstruction in the esophagus to the passage of solid food. Two weeks later there was complete esophageal obstruction for a day, and following this he was able to swallow only small quantities of warm milk, taken slowly.

The general physical examination and the ordinary laboratory tests revealed nothing of significance. Roentgen-ray examination of the esophagus suggested the possibility of a benign tumor because of a filling defect in the middle third of the organ, with a regular contour and a split in the column of barium as it passed around the obstruction, leaving the outline of the esophagus intact (Fig. 2).

Esophagoscopy revealed a huge, soft, brown tumor arising from

* Submitted for publication, May 3, 1926.

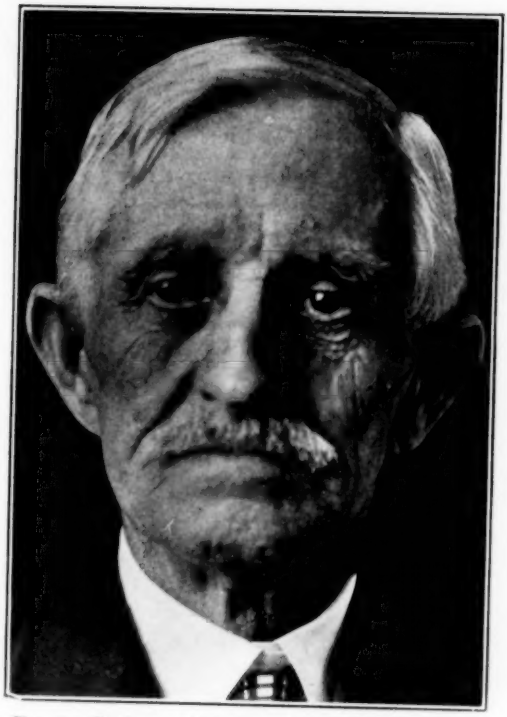

FIG. 1.—Patient with hemangioma of the esophagus.

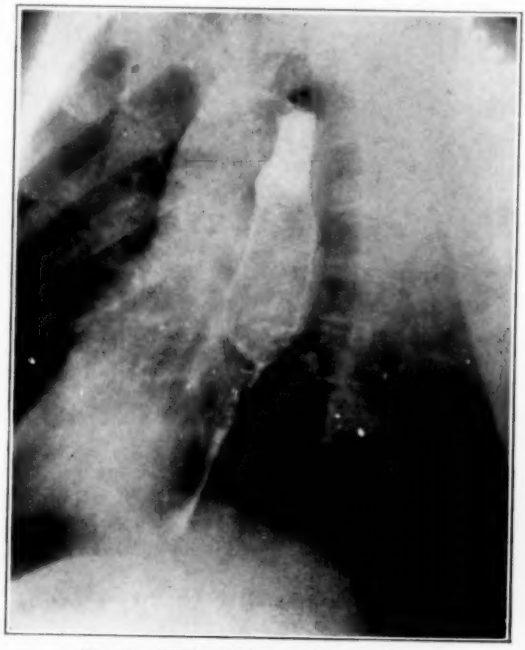

FIG. 2.—Filling defect in the esophagus.

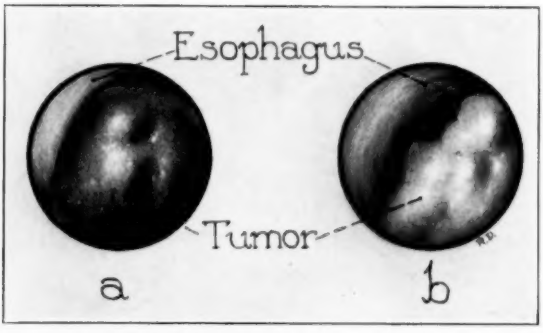

FIG. 3.—*a*, Appearance of tumor at first esophagoscopy; *b*, appearance of tumor after irradiation.

FIG. 4.—Photomicrograph of tumor.

the posterior wall of the middle portion of the esophagus (Fig. 3*a*). A specimen removed for microscopic study proved to be a hemangioma (Fig. 4). It was impossible to introduce the esophagoscope beyond the upper margin of the growth without producing undue trauma. After five days a second esophagoscopic examination was made, and radium treatment was applied. The radium applicator, made of brass, walls 0.75 mm. thick, was similar to the ordinary

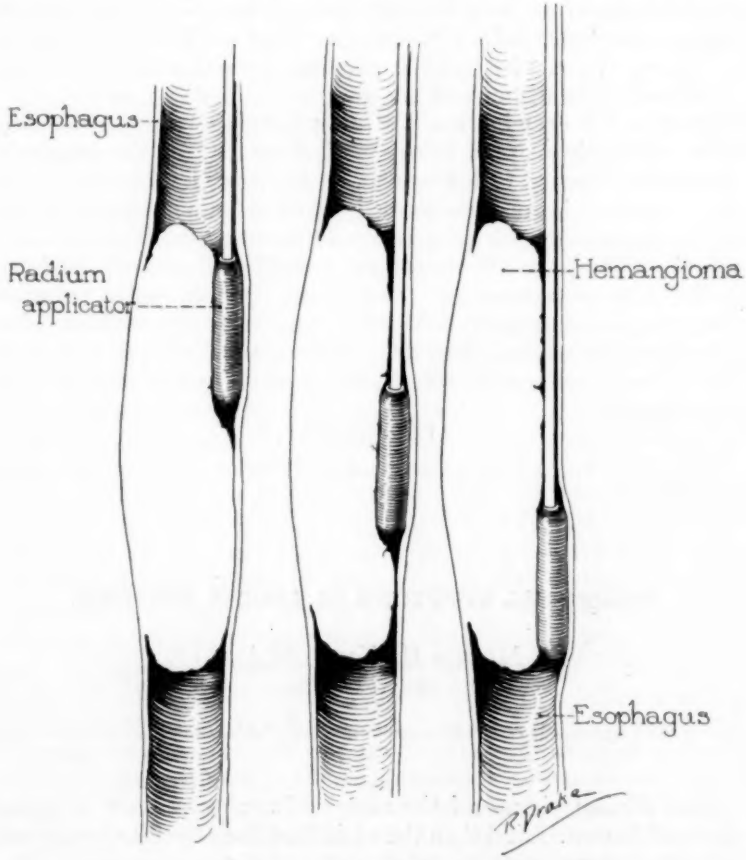

FIG. 5.—Method of applying radium to the tumor.

universal silver tube containing 50 mg. of radium element (sulphate). The cap of the radium container was removed and a flexible stem (solder wire, 60 cm. long) to which a similar cap had been soldered was put in place. This could be held in position during the time required for treatment. For the first application 55 mc. of radon was used. It was filtered through the wall of the container and 3.8 mm. of Para rubber (tubing), and held in one position for one

hour. The area exposed was about 2 cm. below the upper margin of the tumor (Fig. 5). The lead stem was bent at the angle of the mouth and then fixed to the attachment of the right ear and secured with adhesive strips; this was readily tolerated by the patient.

The dysphagia was partly relieved the day after treatment. A second treatment was given four days later. Two areas were exposed, one at a time, and the same container with 49 mc. of radon, and the same filtration were used. The time, however, was three-fourths of an hour for each area. The two treatment fields exposed the lower half of the tumor. The applicator was placed by direct vision. In treating the last area the applicator was withdrawn for a distance of 2.5 cm.

At the next examination, five days later, the tumor was found to be markedly reduced in size, and about half of the remainder was easily removed with forceps. It was possible to introduce the esophagoscope beyond the lower limit of the tumor, about 10 cm. of the esophagus being involved by the growth. Immediately after this the patient was able to eat any type of food without difficulty. At the final esophagoscopy, three weeks after the initial examination, the remaining portion of the tumor was pearly white and had a cooked appearance (Fig. 3*b*). The patient was permitted to return home, and was instructed to report for examination again in four months.

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PRODROMAL SYMPTOMS IN ANGINA PECTORIS.

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The clinical picture of the attack of angina pectoris is typical and well known. And even the variations from the usual have been clearly set down.

In this analysis of 82 patients who have been under careful observation for a varying period of time, I want to call attention to certain clinical features that are more particular in their significance.

The attack itself is so characteristic that it hardly needs description. Major attacks have been described as follows: Origin under the sternum, often at the junction of the first and second thirds of the bone, and a sense of constriction or compression, as if the chest were in a vise, or the breast bone crushed inward by an iron bar.

This pain may come in any degree, from a transient sense of tightness or oppression about the upper sternum, to utter torture. A third feature is a tendency to radiate from the midsternal origin into sections of the brachial plexus, in the first instance, of the left side, but occasionally of the right also—rarely of the right alone. These attacks are characteristically brought on by effort, by cold, and the like.

Angina pectoris is essentially a symptom complex, and in its name does not include the underlying morbid processes. It is associated particularly with sclerosis of the root of the aorta and changes in the coronary arteries.

It is difficult clearly to conceive the anatomic change that takes place to produce the first or even later attacks of angina pectoris or the physiologic mechanism by which it subsides. The effect of nitrites is as spectacular and phenomenal in relieving the attack as that of adrenalin in bronchial asthma.

A number of theories have been conceived as to the immediate cause of the attacks. One assumption is that the symptoms are the result of heart-muscle strain with extreme tension of the ventricular walls consequent upon structural changes in the muscles. Heberden, who first described the condition, believed, on the contrary, that it was a cramp of the heart muscle itself.

Another conception so strongly defended by Allbutt is that the symptoms in angina pectoris result from changes in the adventitia of the aorta without involvement of the heart muscle.

Other theories of the attacks have for their basis involvement of the coronary arteries. This involvement may be either of organic origin, such as narrowing or thrombosis of the vessel, or, of physiologic origin with spasm or constriction of the coronary branches and a resulting transient ischemia of the heart muscle.

Reasoning on pathologic principles, we cannot assume extensive aortic change without conceding the probability of a parallel or contiguous effect in the coronary branches; this again leads to the tacit implication of a consequent change in the myocardium. Although the muscular affection may not be demonstrable in every case, its absence cannot, with any certainty, be determined. And pain need not be attributed to one morbid process alone. We must, therefore, accept the possibility of all these factors in different cases.

The present study is based upon the analysis of the histories of 82 cases of undoubted angina pectoris with typical attacks, observed over a long period of time, with careful clinical and electrocardiographic studies. From this study, one is led to the conviction that atypical prodromal attacks and prodromal symptoms should be recognized as an integral part of the clinical picture of angina pectoris.

It is the particular purpose of this paper to call attention to these prodromal symptoms and prodromal attacks in cases that eventually present the unmistakable features of angina pectoris.

These premonitory symptoms are divisible into several groups:

1. Prodromal attacks in angina pectoris.
2. Substernal burning sensation, "heart-burn."
3. Attacks of epigastric pressing pain or epigastric burning sensation ("acute indigestion").
4. Dyspnea, palpitation and fatigue on moderate exertion with other signs and symptoms indicating myocardial impairment.
5. Cardiac asthma with pulsus alternans.
6. Cerebral thrombosis.

Prodromal Attacks. In 4 cases, the attack so typical of angina pectoris was preceded by symptoms and attacks which do not bear the characteristics of angina; yet their evident association with the disease entitles them to a place as part of the picture. In these cases the first attack noted by the patients indicated some sudden cardiac change and consisted of sudden weakness, faintness, or darkness before the eyes, falling to the ground without loss of consciousness, and without any chest pain. In subsequent attacks, the pain became the predominating feature.

Case Reports. CASE I.—H. F. A. gave a history of untreated syphilis and a 4 + blood Wassermann test. At the age of forty-four years, while at work, he suddenly weakened and fell to the ground, but was not unconscious; he was relieved after two hours. He had no pain in this nonanginal attack. Two and a half years later, an attack recurred with pain in both wrists radiating down to all the finger tips, up the arms and across the chest and dorsal spine. This patient had syphilitic aortic disease with regurgitation and severe angina pectoris.

CASE II.—M. F., aged thirty-nine years, complained of some dyspnea and palpitation on exertion for five years. One day, after moderate exertion, he had an attack of sudden darkness before the eyes with palpitation and a sensation as if something dropped in the chest. He did not fall unconscious and had no chest pain in this attack, but became pale and recovered after ten minutes. After resting a few days, he continued at his work as chauffeur until four months later, when he had a typical attack of severe angina pectoris.

CASE III.—R. B., at the age of forty-five years, had an attack of precordial pain, pressing and nonradiating, which was relieved after two or three hours. No further symptoms were suffered from until a year later when a typical attack of angina pectoris took place.

CASE IV.—M. B., recalls that at the age of forty-two years, he had a sudden pain in the middle of the chest which was relieved in a short while. Since then he suffered dyspnea and a burning sensa-

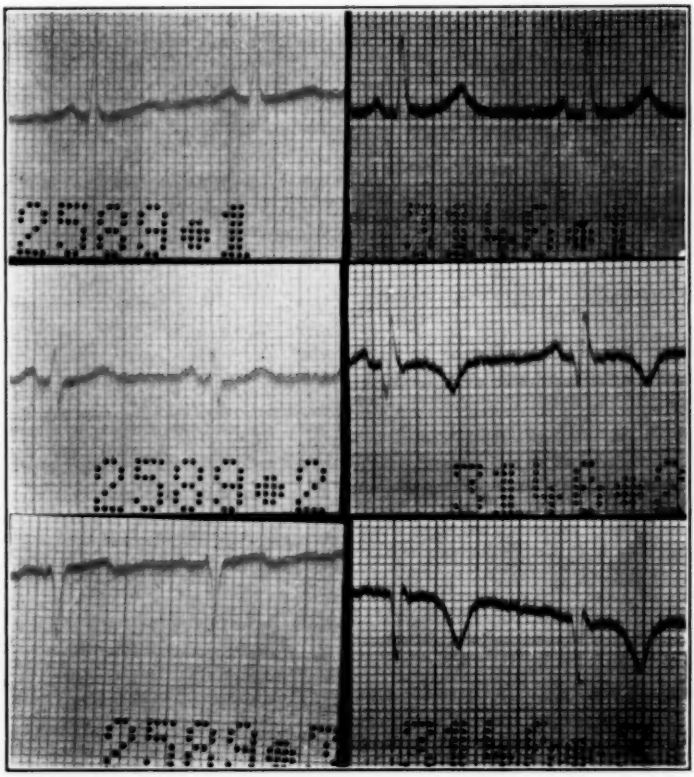

FIG. 1.—Case H. B, No. 2589. Six months after onset of pain; No. 3146, eight months later; one week after first attack.

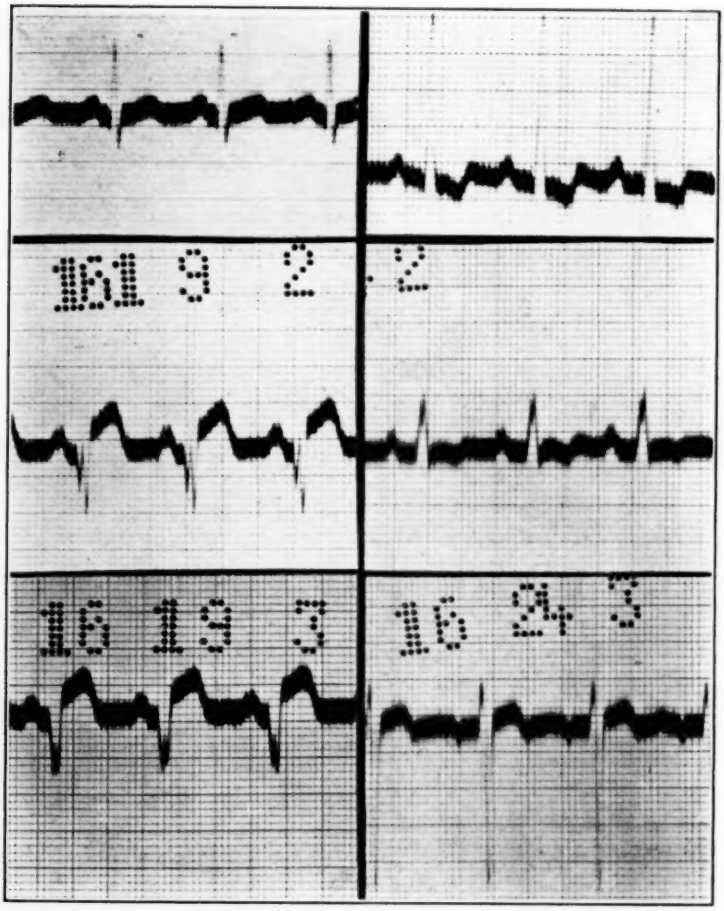

FIG. 2.—Case P. B., No. 1619. Four weeks after onset; No. 1624, ten days later.

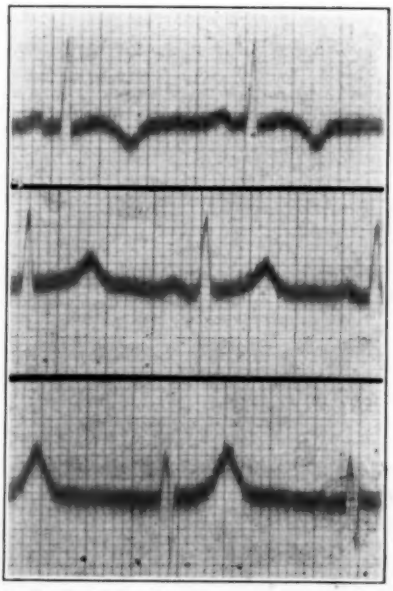

FIG. 3.—Case N. L. F., No. 1816. Two weeks after first severe attack.

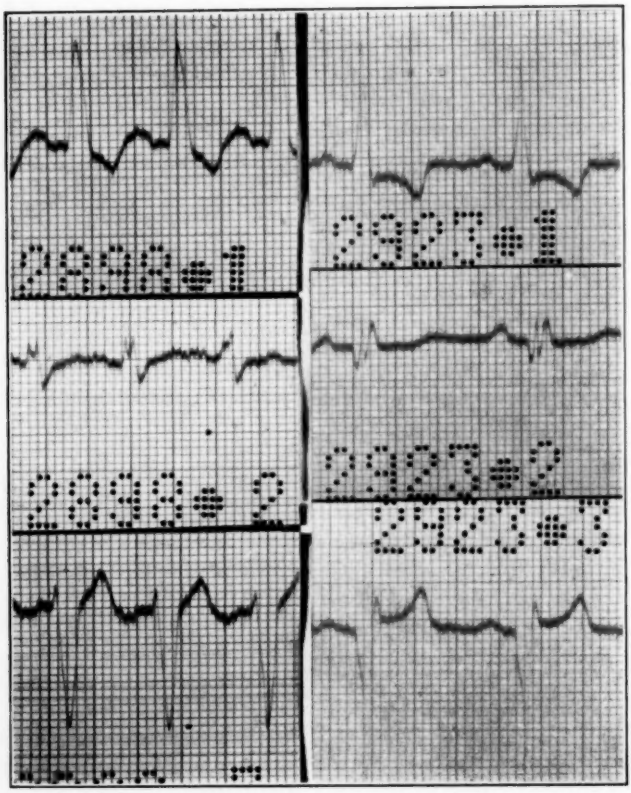

FIG. 4.—Case L. F., No. 2898. Cardiac asthma three years. Pulsus alternans. Case I. P., No. 2923. Cardiac asthma one and a half years. Pulsus alternans; one and a half years after first anginal attack.

tion over the manubrial region after moderate exertion. His first attack of severe typical angina pectoris occurred eight years later.

Substernal Burning Sensation. A more characteristic symptom, which persisted in a group of cases over a long period of time, and is as distinct evidence of the pathologic process going on behind the sternum as the anginal attack itself, is what the patients desscribed as a "burning sensation" or " burning pain" behind the sternum. This may be constant in the sternal region or may spread over the precordium and even to the back. Sometimes it is brought on by exertion, sometimes only by bending over, without any radiation and without any particular reference, otherwise, to the heart.

A steady manubrial pain over a long time, or a continuous burning sensation should, therefore, be a warning signal in questionable cases. It is important to remember this symptom as part of the picture of angina pectoris (Fig. 1). The following cases illustrate this prodromal symptom:

CASE V.—P. B., aged fifty-one years, complained for four weeks of a constant burning sensation behind the sternum and about the precordium with pain across the middle of the back. His heart showed electrocardiographic evidence of myocardial changes (Fig. 2). Two weeks later, he had a severe attack of substernal distressing pain with restlessness, inability to breathe, anxious facies, and profuse perspiration—a typical attack of angina pectoris. His breathing became very difficult, rales spread over both lungs, the heart rate was 70 with an occasional extrasystole, and death took place with pulmonary edema in one hour. The burning sensation had been considered a possible gastric symptom and gastric analysis had even been made.

CASE VI.—M. B., since the age of thirty-one years following an attack of acute articular rheumatism, suffered for five years from a steady manubrial pain and occasional attacks of fainting, before his characteristic angina developed.

CASE VII.—K. L., at the age of fifty-two years, had a severe attack of angina pectoris; but for one year before that she had been suffering from a burning sensation in the midsternum radiating to both shoulders and directly through to the back only after walking one block, or up an incline, or when bending down. The latter movement was associated with a feeling of dizziness. This burning sensation disappeared when she was seated or lying down.

CASE VIII.—L. C., aged fifty-seven years, complained of epigastric distention, sour belching and heart burn after eating. For

six months prior to his first typical attack of angina pectoris, he complained of vague precordial sticking pain on deep breathing at times. This pain was associated often with belching and epigastric pressure and radiated directly through to the back. Only when the attacks became typical across the chest was the pain also felt in the left arm.

Epigastric Pressing or Burning Sensation. The pain preceding typical attacks of angina pectoris is, in some cases, located in the epigastrium. These symptoms often focus attention to the stomach, sometimes for a long period, before the actual condition is discovered. In fact, in a good many cases the complaint was considered referable to the stomach and special gastric studies were made.

The particular emphasis brought out by these prodromal symptoms is to indicate the nerve mechanism by which pain is produced from the aorta-coronary artery area.

Attacks of epigastric pain sometimes described as "acute indigestion" may be included in this group of prodromal symptoms. In some cases a distressing pressing sensation in the pit of the stomach follows eating and, in 1 of my cases persisted for four years before the cardiac symptoms developed.

CASE IX.—N. L. F., aged fifty-four years, for years complained of heart burn for which he took bicarbonate of soda. He had attacks of pressing pain in the epigastrium years ago which were treated by colonic irrigations. For two weeks before he first came under my observation, he had sticking pain across the middle of the chest radiating to the left arm. In this case I observed the first typical attack of angina pectoris, but the patient considered it the worst attack of "acute indigestion" he had had. The electrocardiogram showed definite coronary closure indicated by the complete inversion of the *T* wave in Lead I with its increased height in Lead III. The electrocardiogram two weeks after this attack of coronary closure is shown in Fig. 3.

CASE X.—D. D. knew of his high blood pressure for one year, but he had precordial pressing on exertion for three weeks without any characteristic attacks. His first attack occurred after these three weeks of premonitory symptoms. Following this first attack, his electrocardiogram showed definite coronary closure.

CASE XI.—M. R., aged fifty-eight years, for one week before he had the first attack of angina pectoris, suffered from a heavy sensation in the epigastrium. This epigastric oppression was severe with belching after meals. Several months before, he had an attack of dizziness while walking, although he never fainted. For a number of years since then he has been under observation for typical angina pectoris.

Case XII.—S. M., aged forty-seven years, complained of heartburn for eight years. During that time he had severe attacks of what he called "acute indigestion" with sudden pain radiating up to his throat. He was free from these for four years, when he suddenly had his first attack of angina pectoris at the age of forty-six years. This patient developed marked pulsus alternans, cardiac enlargement, with the possibility of aneurysm of the left ventricle. He died two years later at the age of forty-eight years.

Dyspnea, Palpitation and Fatigue on Moderate Exertion. In some cases, for a more or less prolonged period there was noted a degree of limitation of function, usually only mild, with shortness of breath on exertion and palpitation at times. These indicate that the cardiac process preceding attacks of angina pectoris is a prolonged process and that the appearance of angina pectoris is a manifestation of an already more or less developed pathology. Soon after the first symptoms of angina pectoris appear, some evidence of myocardial damage is already to be found in the electrocardiogram. This would imply rather early involvement of the coronary arteries causative of the anginal symptoms.

Case XIII.—E. H., aged forty years, noticed for one month that he was fatigued more than usual toward the end of the afternoon after his day's work. His first attack of angina pectoris occurred subsequently after ascending a hill.

Case XIV.—J. K., aged forty-nine years, complained of slight dyspnea and palpitation on exertion for six months. The first attack of coronary thrombosis occurred then, after which he began to have substernal pressing pain after walking one or two blocks, which was relieved by rest.

Case XV.—R. L., aged sixty-three years, had dyspnea and palpitation on exertion for two years with edema of the legs. She then had a sudden severe attack of angina pectoris radiating down the left arm and wrist.

Case XVI.—E. L., aged fifty-two years, had moderate palpitation and dyspnea on exertion for several years before her first attack of angina pectoris.

Cardiac Asthma with Pulsus Alternans. In 3 cases of this series, the symptoms were predominantly those of cardiac asthma. In 1 of these, the asthma developed two years after the occurrence of typical attacks of angina pectoris. In the other 2, recorded below, the cardiac asthma preceded for a long time the symptoms of angina pectoris. In fact, in both these patients the question of essential asthma was considered by the family physician, and diagnosis was

first made after consultation. These cases had certain factors in common: (1) The first attack consisted of sudden dyspnea with wheezing in the chest and without any cardiac pain; (2) the blood pressure in both cases, systolic and diastolic, was elevated; (3) marked pulsus alternans was present; and (4) the electrocardiogram in both cases showed extensive myocardial degeneration producing right bundle-branch block (Fig. 4).

CASE XVII.—I. P., a carpenter aged fifty seven years, had had one and a half years before, an attack of cyanosis with severe dyspnea, pallor, sweating and pink expectoration. This lasted for a half hour and was relieved by a hypodermic of morphin. This recurred after one year and then more frequently. He now has pressing pain in the precordium, especially during the night, with asthmatic wheezing toward the end of the attack. His pain in the precordial region and weakness of his legs become marked after walking one to two blocks. The electrocardiogram is shown in Fig. 4.

CASE XVIII.—L. F., aged fifty-eight years, had attacks for three years of dyspnea, especially at night with wheezing in the chest, often continuous. Her anginal pain began some time after the asthma with attacks of aching pain over the sternum and right half of the dorsal region. These lasted from several minutes to a half hour, with extreme dypsnea and cold sweat. They occurred at first monthly and at the present time occur two or three times daily.

Cerebral Thrombosis. In some cases coronary sclerosis or thrombosis are incident in the process of general arterial change, atheromatous, senile or arteriosclerotic.

In 4 cases of this series cerebral thrombosis with hemiplegia was associated with angina pectoris. In two of these, however, the cerebral thrombosis preceded the development of typical anginal symptoms and in that way were prodromal to the coronary-artery change.

CASE XIX.—L. L. P., a banker, had his first attack of sudden right hemiparesis, with rapid recovery at the age of fifty years. The first attack of angina pectoris occurred six months later and regularly after that on walking one or two blocks even on level ground. The blood pressure in this case was 200/114, but there was no pulsus alternans. Aortic regurgitation developed three years later and the patient died with an attack of angina pectoris at the age of fifty-four years.

CASE XX.—C. J., aged fifty-four years had slight pains in her chest for several years with dyspnea and palpitation on exertion

for two years and edema of the feet. At the age of fifty-two years, she had a sudden attack of dizziness and motor aphasia which lasted about a month. This was evidence of an arteriosclerotic process in the brain. At the age of fifty-four years, she had her first attack of angina pectoris with severe sudden pain in the precordium radiating to the left axilla. Her blood pressure was 260/154.

Conclusions. The group of cases presented in this paper is sufficient to point out the importance of premonitory symptoms in angina pectoris. Of the 82 cases, there were 25 (30 per cent) who presented prodromal symptoms.

The largest number fall into Groups 2 and 3 (substernal or epigastric burning sensation). There were 10 cases (12 per cent) in these groups. In a few of these, the symptoms of burning manubrial pain and epigastric pressure were combined.

Four cases (4 per cent) had attacks which were nonanginal in character. In 1 case, the attack occurred eight years before the angina. In the interval, however, there was continued burning sensation in the manubrium with dyspnea after moderate exertion, indicating a pathologic process going on for a long time.

There were 2 cases each in Groups 5 (cardiac asthma with pulsus alternans) and 6 (cerebral thrombosis) with very marked prodromal symptoms before the angina manifested itself.

There were 7 cases (8.5 per cent) presenting prodromal symptoms of dyspnea, palpitation and fatigue on moderate exertion with other signs and symptoms indicating myocardial impairment before development of angina pectoris.

It is, therefore, evident that the pathologic process which eventually produces the symptoms of angina pectoris is a prolonged one; that there is early involvement of the aorta and coronary arteries long before the anginal symptoms develop. It is therefore important, in the prevention of angina pectoris, to give careful study and attention to premonitory symptoms such as are described in this communication.

THE RECTAL ADMINISTRATION OF EPINEPHRIN.

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Epinephrin is one of the most commonly used drugs and yet its chemical and physiologic nature make its effective administration

difficult. It is, therefore, of interest that comparatively few studies have been made of its effect by oral and rectal administration in man. Eggleston[1] in a plea for a study of the absorption of drugs in general, states that investigations of the absorption from the rectum have been even more meager than those concerned with absorption from other channels. The effect of epinephrin by oral administration is being studied[2] and the present observations on its effect by rectal administration have been made concomitantly.

Standard textbooks of pharmacology and therapeutics have been consulted regarding the administration of epinephrin by rectum and with one exception no mention was found. Hatcher and Wilbert state that epinephrin is absorbed from the mucous membranes, specifically including the rectum with other mucous surfaces of the body.[3]

The periodical literature contains few reports of observations of this method of administration. The early studies of Bodenhamer[4] and Paradies[5] on the rectal absorption of drugs in general, did not include any form of suprarenal extract. Binet[6] briefly states that the drug was found to be toxic when given by rectum. Lesné[7] made a study of its administration by mouth and by rectum in man and in the rabbit. When administered to children by rectum 2 mg. doses or to adults in 4 mg. doses, it provoked a vasomotor response comparable to that of intravenous infusions in experimental animals. In some cases, there was a slow rise in blood pressure reaching its maximum in fifteen to twenty minutes, and in some cases a slight fall was observed. He advises giving epinephrin by rectum rather than by mouth, as the effect will be much greater and with a smaller dose.

Hoskins[8] administered epinephrin by rectum to cats and dogs, recording the blood pressure and intestinal peristalsis. The drug in doses of from 1 to 5 mg. produced either no effect or relatively slight effects. In positive reactions, peristalsis was depressed and blood pressure either augmented or depressed, the effect persisting from three minutes to an hour in various cases.

In 1921, Muirhead[9] published some interesting observations on himself. The writer, a teacher of pharmacology, became ill with Addison's disease. His principal medication was adrenalin administered hypodermically and by rectum. By the latter method, the sphygmomanometer showed a beginning rise in systolic blood pressure after twenty-five minutes, reaching its maximum after forty-five minutes, and falling to normal in about ninety minutes. He used 2 cc. of a 1 to 1000 solution diluted with normal saline, administered twice daily for several months. However rectal injections had to be abandoned later because of severe rectal tenesmus. Clinically he improved.

A study of the comparison of rectal and colonic injections of epinephrin in rabbits was made by Barbour and Rappoport[10] in

1921. This drug was chosen because there was no record of epinephrin having been tried rectally and because of its specific effect on the liver producing glycosuria. It was considered possible that while rectal as compared with colonic administration might exhibit a greater circulatory effect, the glycosuria would on the other hand, be found less intense, owing to the delay and quantitative diminution of the drug reaching the liver. They found epinephrin was absorbed from both rectum and colon; that from the rectum it caused a greater rise in blood pressure but less glycosuria and diuresis than when injected into the colon.

Lesné[7] in attempting to explain the greater effect of the drug by rectal administration as compared to oral, suggested that through the wealth of anastomoses of the hemorrhoidal veins the drug might pass directly to the vena cava system, and so avoid destruction in the liver. Barbour and Rappoport's work would lend support to this theory. However Levy[11] has more recently made some interesting observations on this point in a study of the rectal administration of digitalis. He gave 15 cc. of a sodium iodid solution, introduced 2½ inches in the rectum, and took roentgenograms at the end of fifteen minutes, two, four and six hours later. The results were interpreted as indicating that even with the exercise of reasonable care in introducing such an amount of fluid, most of it finds its way at once into the lower loops of the sigmoid and is absorbed from this portion of the intestine. A relatively small amount remains in the upper portion of the rectum and an even smaller amount is absorbed from that part drained by veins which empty directly into the inferior vena cava. This worker holds the opinion that digitalis given by rectum is taken into the venous circulation for the most part by way of the mesenteric and portal systems.

Lesné and Baruk[12] administered rectally 100 drops of a 1 to 1000 adrenalin solution in children between ten and fourteen years of age and obtained a pulse rise and slight tension increase in ten to fifteen minutes without glycosuria. They were unable to obtain similar results by oral administration. In very young children, they noted the appearance of extrasystoles.

Present Study. The writers have attempted to determine the effect on the blood pressure of epinephrin by rectal administration in man. The results are based on 31 observations made on hospital patients whose state of health was regarded as having no effect on the results. The general method used was the same in each case. The patient was kept resting in bed for at least six hours before the test was made. Several control blood pressure and pulse readings were made, and then the administration of 10 cc. of tap water introduced 6 inches in the rectum. The tube was left in place and blood pressure and pulse readings were made over a period of thirty minutes. Four milligrams of epinephrin (adrenalin tablets, Parke, Davis & Co.,) dissolved in 10 cc. of tap water was

then introduced and the tube removed, after which the blood pressure and pulse readings were made at three- to five-minute intervals over a period of at least one hour and several times as long as three hours.

Of the series of 31 observations 3 were unsatisfactory, due in 2 cases to poor coöperation from the subject and in the third instance to defecation twenty minutes after the drug had been given. The effect on the blood pressure is shown in tabular form:

TABLE I.

Amount of blood pressure rise.	Number of cases showing blood-pressure rise.	
	Systolic.	Diastolic.
0 to 10 mm.	10	16
11 to 20 mm.	4	10
21 to 30 mm.	8	1
31 to 40 mm.	5	1
Over 40 mm.	1	0

Thus in 64 per cent of the 28 satisfactory observations, there was a rise in blood pressure of over 10 mm. of mercury and in view of the negative results of the same amount of water given rectally as a control in each case, these results probably indicate the effect of the drug. In 50 per cent of the cases, the rise was over 20 mm. This rise in blood pressure is generally delayed, the maximum figure occurring usually between twenty and fifty minutes after its administration. In 6 cases it was under twenty minutes and in 8 over fifty minutes, the longest being ninety minutes. Associated with this slower action, the blood pressure remains elevated over a relatively long period. In every case in which the rise was 20 mm. or more, it required forty-five minutes as the minimum time to return to the basal blood pressure. Several observations were stopped after one hundred and forty minutes with the blood pressure still elevated above the control level. This effect, then, usually persists much longer than when the drug is given intramuscularly or intravenously. As is shown by the above table, the effect on the diastolic pressure is much less than on the systolic pressure.

The pulse rate was little affected; in 6 cases it fell between five and ten beats per minute; in 12 other cases it remained unchanged or decreased less than five beats. In the remaining cases, it was increased, only 4 of which increased more than ten beats per minute, the highest being sixteen.

Other subjective effects observed and their frequency of occurrence were: Tenesmus, 17 cases; desire to urinate, 7 cases; abdominal cramps, 5 cases; sweating, 5 cases; epigastric distress, 5 cases; respiration easier, 5 cases; rectal sensations (gas, burning), 4 cases; dryness of mouth, 2 cases. Nausea and vomiting each occurred once. The desire to defecate was present in 55 per cent of the cases at some time during the observation. In 1 case the patient successfully defecated and 4 others made unsuccessful attempts, suggesting

that the tenesmus resulted from direct stimulation from the adrenalin. Without exception this desire passed away, usually before the blood pressure returned to its former level. In 3 cases, the patient urinated. It was considered that the rectal cramps and desire to defecate might account for some rise in blood pressure. However in 2 cases this symptom was very marked without any change in the blood pressure.

It is of interest to note that in 5 cases of chronic asthma, every patient obtained prompt effective relief in his respiratory difficulty.

The results in different cases vary somewhat and the data are given here on only 1 case to serve as an illustration:

TABLE II.

(J. L., a man, aged fifty years; diagnosis, alcoholism; basal metabolism +8.)

Time.	Time Interval.	Blood pressure. Systolic.	Diastolic.	Pulse.	Notes.
7.40	...	112	66	68	
7.45	...	110	66	70	
7.50	...	110	68	70	
7.50	Given 10 cc. tap water 6 inches in rectum				
7.55	5	108	70	70	
8.00	10	112	70	74	
8.05	15	108	68	70	
8.10	20	112	70	70	
8.15	25	108	70	72	
8.20	30	110	68	72	
8.20	Given 4 mg. adrenalin in 10 cc. tap water 6 inches in rectum				
8.23	3	112	72	72	
8.27	7	114	74	70	
8.31	11	112	72	70	
8.37	17	116	74	72	
8.43	23	120	78	70	
8.46	26	124	82	70	
8.49	29	126	78	70	Slight desire to defecate
8.52	32	128	80	68	
8.57	37	132	82	68	
9.01	41	136	80	66	"Cramps" in lower abdomen
9.05	45	138	84	68	
9.10	50	142	82	68	No distress
9.15	55	144	84	67	
9.20	60	144	80	66	No distress and no straining
9.25	65	140	82	66	Sweating; still has desire to defecate
9.30	70	146	86	68	
9.35	75	144	84	66	
9.40	80	138	80	70	
9.45	85	140	80	70	
9.50	90	142	80	70	Less desire to defecate
10.00	100	136	80	72	
10.10	110	130	76	70	Following this point the patient made an unsuccessful attempt to use bedpan
10.30	130	142	80	70	Defecated
10.40	140	130	76	74	
11.00	200	118	72	72	Quiet; no sensations
11.15	215	114	72	74	

Summary. 1. In 31 observations of the effects of the rectal administration of epinephrin, 64 per cent showed a blood pressure rise of over 10 mm. and 50 per cent a rise of over 20 mm. of mercury.

2. The maximum effect is reached in an average time of forty minutes after administration. The duration of the blood pressure rise in effective cases is forty-five minutes or longer.

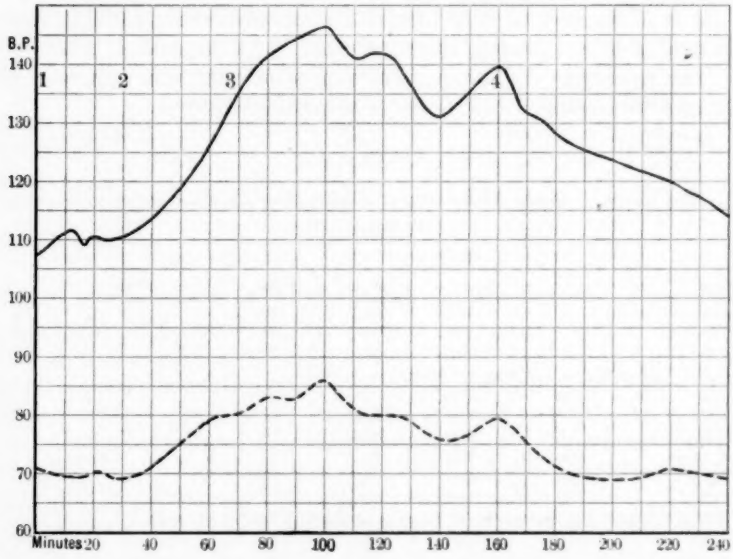

CHART I.—Effect of 4 mg. of epinephrin on the blood pressure administered rectally, 6 inches within the rectum: Solid line, systolic; broken line, diastolic; BP, blood pressure; 1, control of 10 cc. of tap water given rectally; 2, 4 mg. epinephrin given rectally; 3, faint tenesmus; 4, defecation.

3. The pulse was slightly decreased or remained constant in 18 cases and increased in 13 cases.

4. Other systemic and local effects most frequently observed were tenesmus, desire to urinate, abdominal cramps, sweating, epigastric distress, and relief of respiratory difficulty in asthmatic cases.

Conclusions. 1. The rectal absorption of epinephrin in relatively large doses is unreliable producing little or no effect in about 50 per cent of cases.

2. Epinephrin is effective by rectal administration in a certain number of cases and in such cases the systemic effect, while slower in reaching a maximum, persists over a much longer time than when given hypodermically.

3. The rectal method of administration should be of advantage in cases requiring a prolonged effect and repeated doses of epinephrin, as in asthma or Addison's disease.

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REVIEWS.

A TEXTBOOK OF UROLOGY. BY OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., Director of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital; and THOMAS JOSEPH KIRWIN, PH.C., B.S., M.A., M.D., Chief of Clinic of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital. Pp. 700; 233 illustrations; 13 plates. Philadelphia: Lea & Febiger, 1926. Price, $10.00.

A TEXTBOOK of Modern Urology in only one volume. When one tries to find the missing material, or compressed chapters, that made this possible he is surprised to find a gain rather than a loss and much traditional rubbish has been jettisoned entirely. The authors have realized that urological technique cannot be taught in print, but only at the expense of time and patience under supervision, therefore, we miss not in this volume chapters descriptive of instruments and their handling. There is a wealth of embryological, anatomical and clinical pathology excellently presented, and made the basis of clinical diagnosis and treatment. The chapters on "the testicle," "the female urethra," and "Cowper's glands" are unusually worthy of consultation. Regional anesthesia is strongly advocated and its technique carefully described. A. R.

A MANUAL OF HYGIENE AND SANITATION. By SENECA EGBERT, A.M., M.D., Dr. P.H., Professor of Hygiene, University of Pennsylvania. Eighth edition. Pp. 616; 158 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $4.00.

THE eighth edition of this well-known book has been thoroughly revised. Two new chapters have been added: Transmission of Disease and Tourist and Vacation Hygiene and Camp Sanitation, the latter replacing the chapter on military hygiene of the seventh edition. The newer knowledge of hygiene and nutrition has been included.

The style of presentation is interesting and the material well chosen. The book deserves wide recognition. J. S.

MATERIA MEDICA AND THERAPEUTICS. By LINETTE A. PARKER, B.Sc., R.N., formerly Instructor in Nursing and Health, Teachers' College, Columbia University, New York City. Fourth edition. Pp. 364; 35 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $2.50.

THIS is a very suitable text for student nurses, because information is given in a clear, brief yet sufficiently comprehensive manner. Drugs are discussed logically, according to the system chiefly affected. The action of drugs might better be observed by students if a description of the appearance of a patient under the effect of the drug were given where it is possible. New drugs, such as novasurol, chaulmoogra oil, carbon tetrachlorid and others not mentioned in older editions are presented. The evils of patent medicines and quack remedies are brought to the student's attention. Some very helpful illustrations and diagrams are given. The book is well indexed and binding and paper are durable and neat. D. M.

PRINCIPLES OF HUMAN PHYSIOLOGY. By ERNEST H. STARLING, University College, London. Pp. 1074; 568 illustrations. Fourth edition. Philadelphia: Lea & Febiger, 1926.

THIS new edition of Starling's textbook has some alterations, though in the main it remains as before. It represents probably one of the best textbooks of physiology written by a single man, but even so it seems doubtful whether the time has not passed when an adequate textbook can be written by one person.

The chapters on the eye (for which Dr. Hartridge is partly responsible) are probably the best in any textbook. The rest of the book is excellent and the chapters on muscular work and on reproduction have been brought well up to date.

On the other hand (as must be the case), other subjects, such as the spleen and pituitary are somewhat inadequately treated and the reviewer also considers that insufficient emphasis has been placed on Dr. Richards' recent work on the kidney, though here too the subject matter has received considerable revision. H. B.

DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., LL.D., F.R.S. Sixth edition. Pp. 1268; 1147 illustrations; 11 colored plates. St. Louis, C. V. Mosby Company, 1926. Price, $12.00.

THE author's sixth edition of his text, *Diseases of the Skin*, is a genuine landmark in the publication of dermatologic monographs.

No American text in this field seems ever to have achieved even a modest fraction of the popularity of this work. The explanation is not far to seek. The author's indefatigable energy, his huge material, his judicious selection, his friends who have contributed photographs and his publishers, who have evidently spared neither effort nor expense on the format of this work, all deserve their share of congratulation. The student is pleased with the visual presentation, the practitioner with the prescriptions and those inimitable odds and ends of valuable therapeutic comment from his and others' experience with which the author has filled his pages. The expert finds valuable clues in the bibliography and the photographs of rarities. As an example of textbook writing according to the teaching technique of the day, this work takes high rank. The successive editions have all shown evidence of the care which has been taken to keep the material up to date and in many respects pictorially unique.

The problem of writing a dermatologic textbook is one of unusual difficulties. The vast spread of the subject, the superficiality which easily creeps into thinking and practice about it, the instinct for the spectacular as distinguished from the type and the true, must all be struggled with in the effort to produce a balanced work. It is to be hoped that a day will come in which more medicine and less dermatology will find its way into such textbooks for students. For example, the presentation of lupus erythematosus disseminatus might well, in this work, have more of a medical and less of a purely morphologic cast. The slavery to wall paper is still evidenced in the miserable colored plates, one here at least bordering on the ludicrous, which publishers seem still to insist on as part of a dermatologic text. But these are after all either quibbles or futures. Today, there can be no question that the author's text deserves its verdict at the hands of the profession as a convincing, informing, accessible and scholarly piece of work. J. S.

EDGAR'S PRACTICE OF OBSTETRICS. By J. CLIFTON EDGAR, M.D., Emeritus Professor of Obstetrics and Clinical Midwifery, Cornell University Medical College. Revised by NORRIS W. VAUX, Clinical Professor of Obstetrics in the Jefferson Medical College, Philadelphia and Obstetrician to the Philadelphia Lying-In Hospital. Sixth edition. Pp. 743; 684 illustrations, including 5 colored plates. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $8.00.

AFTER a period of ten years a new edition of the author's *Practice of Obstetrics* is brought forth under the revising pen of Dr. Vaux. The book is materially reduced in both text and illustrations. To

offset this pruning short references to many of the advances in this branch of medicine have been added. One feels that in certain subjects these newer ideas might have been given in more detail or, for instance, in extraperitoneal Cesarean section a modern method might have entirely displaced the old text and illustrations. The frequent evidences of lack of proofreading might not satisfy a purist.

P. W.

HANDBOOK OF DISEASES OF THE RECTUM. By LOUIS J. HIRSCHMAN, M.D., F.A.C.S., Professor of Proctology, Detroit College of Medicine. Fourth edition. Pp. 403; 257 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $6.50.

DEALING only with those anorectal conditions which may be treated nonoperatively or by operation under local or regional anesthesia, this well-known handbook is a valuable guide to the practitioner of medicine or of general surgery. The text is orderly, practical and explicit; the illustrations numerous, clear and helpful. The present edition differs from its predecessor chiefly in the omission of the chapter upon examination of the feces, the addition of a description of the technique of sacral anesthesia and a revision of the chapter, written by Dr. John L. Jelks, on dysentery. Several new illustrations, chiefly roentgenograms, have been added.

R. G.

BLOOD CHEMISTRY: COLORIMETRIC METHODS. By WILLARD J. STONE. Second edition. Pp. 123; 7 illustrations. New York City: Paul B. Hoeber, 1926. Price, $3.25.

THE second edition of this book contains appropriate methods of blood chemistry arranged in a concise manner with comments of clinical importance as to their interpretation of the biochemical data. In addition, there are kidney functional tests and suggestions for the dietary treatment of metabolic diseases. Well-known dietary data tables are included. The book is designated for the general practitioner, but there is some doubt of his ability to use this or other similar books to develop his technique without special laboratory training.

W. K.

A BIPOLAR THEORY OF LIFE. By GEORGE W. CRILE, M.D., Western Reserve University. Pp. 405; 62 illustrations. New York: The Macmillan Company, 1926.

THIS book is devoted to an attempt to prove the following theory:

"If the brain and liver are the positive and the negative poles of the organism, then certain conditions would follow from this interrelationship: The brain and the liver would work together, would together show specific changes as the result of work, would together be restored by sleep. This condition has been supported by histologic and by physical researches.

"Although, as we believe, the specific activities of muscles, glands, etc., are carried on by minor circuits, nevertheless, unless the grand circuit between the brain and liver be kept intact and active, life cannot continue."

Although no one could question the author's standing as a surgeon, the evidence put forward in favor of this revolutionary theory is quite inadequate even to allow consideration of it as a possibility. H. B.

YOUNG'S PRACTICE OF UROLOGY. By HUGH H. YOUNG, M.D., and DAVID M. DAVIS, M.D., with the collaboration of FRANKLIN P. JOHNSON, M.D. A Practice of Urology in Two Volumes. Pp. 1484; 1000 illustrations, 20 being color plates, by William P. Didusch. Philadelphia: W. B. Saunders Company, 1926. Price, $25.00.

DR. YOUNG, long recognized as the dean among American urologists, presents, in collaboration with Drs. Davis and Johnson, a practice of urology, which, as the name indicates, is *Young's Practice of Urology*. Whatever shortcomings, if any, the books may have, are perhaps to be attributed to faults apt to be inherent in a too highly personalized scientific work.

These volumes are based on experience gained in the study and treatment of 12,500 individuals with genitourinary diseases, from which innumerable analytical deductions are drawn, and upon the basis of which, opinions, not always entirely devoid of dogmatism, are expressed. The obvious purpose of the work is to record a most extensive personal experience, and the result is a monumental contribution to urologic literature.

In some instances the tone becomes a trifle argumentative, especially in defense of the intravenous use of mercurochrome and of the author's priority in the development of perineal prostatectomy. Diverse opinions are usually given due consideration, but the conclusions drawn from original work are sometimes lacking in the modest interpretation of results that may conceivably lack finality.

The book is built on the foundation of many contributions to the literature by the author and his coworkers in the past; it elaborates and gives in most minute detail a final analysis of the experience upon which these excellent literary and scientific contributions have

been based. It is to be expected that the result is a colossal work of infinite value.

Those whose interest in urology is merely the part of a general interest in surgery may find some fault with the work for purposes of reference, since little effort has been made to collate the facts pertaining to a given condition. There is nothing that would remotely identify these volumes with textbooks as a class. The work will be used largely for reference purposes no doubt, but not always with complete satisfaction. As textbooks for undergraduate students, they are far too comprehensive and, perhaps, somewhat lacking in an essential breadth of view. The postgraduate student, however, will find the work invaluable as the easily available source of urologic practices followed in the foremost American clinic.

The arrangement of the subject matter is unique, and of such a character that considerable repetition is inevitable. Thus, in Vol. I 67 pages are devoted to the subject of obstructive uropathy, which deals largely with pathologic changes due to urinary stasis and, while the causes and complications of stasis are discussed at some length a far more comprehensive discussion of the latter is reserved for separate sections.

The text throughout is most complete but not always free from irrelevancy, and there is at times some difficulty in locating the subject matter in its entirety. Thus, the index refers to several pages devoted to acute gonorrheal urethritis, but scattered throughout the text are many pages devoted to gonorrhea and its complications.

The major portion of the second volume is devoted to operative urology, and this section of the work is invaluable, inasmuch as the technical procedures adopted by the senior author, are described in detail and very well illustrated. The section on congenital anomalies, likewise a part of the second volume, and comprising 136 pages, is most complete.

The reviewer has gained the impression after spending many productive hours with these volumes that, in order to extract the full measure of their value, it is necessary to read each section in its entirety and to hope to find in sequential order all of the facts pertaining to any given disease or condition. This is rather time consuming, but we can conceive of no better use to which the time of the urologist could be put.

Urologists the world over will welcome this work from the hand of a master whose leadership in the field of urologic surgery has long since been recognized; they will find some things to criticize perhaps, especially the arrangement of the subject matter, but this will be overlooked in contemplation of a maze of information to be gained from the discussions founded on the analysis of an enormous experience. The books are a tribute to the indefatigable labors of

many men, and especially of the senior author, not the least of whose contributions to the science of urology, has been an ability to inspire others to notable achievements. L. H.

DIATHERMY: WITH SPECIAL REFERENCE TO PNEUMONIA. By HARRY EATON STEWART, M.D., Consultant in Physiotherapy, H. S. V. B. Hospital, New Haven, Conn. Second edition. Pp. 221; 45 illustrations. New York: Paul B. Hoeber, 1926. Price, $3.00.

DOES diathermy lower the blood pressure in pneumonia? From a series of 159 cases, very carefully and accurately studied, this question can be answered emphatically, No. The blood pressure taken before and after treatment in each case showed little change. Sputum typings and other laboratory procedures, which are given in detail, lend an air of great scientific accuracy to this report. A series of 21 control cases had a mortality of 42.9 per cent, while a series of 47 cases treated by diathermy during the same period had a mortality of 17.1 per cent. Unfortunately only 10 pages are devoted to surgical diathermy. This invaluable method of treating malignancy has always been inadequately treated. P. S.

ARCHIVES OF THE ANDREW TODD MCCLINTOCK MEMORIAL FOUNDATION FOR THE STUDY OF DISEASES OF THE ALIMENTARY CANAL. VOL. I: PLEOMORPHISM IN BACTERIAL PROTOPLASM; A STUDY IN PSITTACOSIS. By ANDREW TODD MCCLINTOCK, M.D. Pp. 240; illustrated. Privately printed, 1925.

THE author, a gifted, resourceful and enthusiastic medical investigator, was born in Wilkes-Barre in 1885 and died in 1923. As a student at the Medical School of the University of Pennsylvania, where the reviewer had the good fortune to know him in classes and medical societies, he not only stood near the top of his class but succeeding in completing research work of value. Following several years in Vienna, Berlin and London, he returned to Wilkes-Barre, where, as internist and pathologist, he forged rapidly ahead, only to be struck down by an obscure intestinal condition, from which he never recovered and which proved fatal after four years.

The memorial, of which this volume is the first fruit, was founded by his wife, to promote bacteriologic and other researches into gastrointestinal disease and to make them available by publications such as the present one, or by such other means as might seem most efficient.

The present study was occasioned by the attempt to connect a certain peculiar epidemic in Wilkes-Barre in 1917 with the occurrence of psittacosis among some sick parrots exhibited at that time. Not only was the connection demonstrated, but it was made the basis for a much more extensive investigation into bacterial mutations, affinities and pathogenicity, which contain much of value. Future publications of this memorial will be awaited with interest.

E. K.

A Textbook of Medical Diagnosis. By James M. Anders, M.D., Professor of Medicine, Medico-Chirurgical College, Graduate School of Medicine, University of Pennsylvania; and L. Napoleon Boston, M.D., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania. Third edition. Pp. 1422; 555 illustrations. Philadelphia and London: W. B. Saunders Company, 1925. Price, $12.00.

When any medical textbook has not been revised for eleven years, the task of revision is necessarily an arduous one. When that textbook covers as wide a field as that of medical diagnosis, the task becomes prodigious. To a large extent, this has been successfully done in the third edition of this work, and a great deal of new material has been added. A number of sections, notably those on physical diagnosis, on the infectious diseases, on electrocardiography and on nervous diseases are particularly well done. On the other hand, some are open to criticism, such, for instance, as the section on diseases of the blood. Some examples are cited: The statement that in pernicious anemia the examination of gastric contents after a test meal is negative; the failure to mention mononuclear leukocytosis in glandular fever, or the oxidase stain for leukocytes and its application in the leukemias; or of thrombocytopenia in purpura hemorrhagica, but claiming its presence in hemophilia. That asthmatics generally show a polycythemia is not the general experience. The authors make frequent and good use of the device of tabulating in parallel columns the symptoms and findings in two or more diseases for the purpose of differential diagnosis. The method is, however, fraught with the danger of leading the writer into making categorical statements that are open to question: For instance, that ascites is absent in chronic generalized peritonitis or the alleged negative test-meal findings in pernicious anemia. Some omissions that may be cited are massive postoperative pulmonary atelectasis, blood-calcium figures in tetany and the relation of that condition to alkalosis. Objection may be made to such statements as these: That "migrain, sciatica and epilepsy are also included among the sensitization diseases," that "intestinal sarcoma is quite often met with in young adults." The illustrations are numerous and are well done.

R. K.

A Textbook of Pathology. By Francis Delafield, M.D., LL.D., sometime Professor of the Practice of Medicine, Columbia University, New York, and T. Mitchell Prudden, M.D., LL.D., sometime Professor of Pathology, Columbia University, New York. Thirteenth edition. Revised by Francis Carter Wood, M.D., Director of the Pathologic Department, St. Luke's Hospital, New York, and Director of the Institute of Cancer Research, Columbia University, New York. Pp. 1243; 828 illustrations. New York: William Wood & Co., 1925. Price, $10.00.

This new edition of a familiar standard work on pathology wisely selects facts and useful theories, omitting the more discursive questions. New matter consists in part of a résumé of recent conceptions of the reticuloendothelial system, of jaundice, infections, lung abscess and bone tumors. There is a happy combination of brevity and completeness in the treatment of the various subjects. The work is unusually comprehensive, thus avoiding a criticism permissible about many English texts. It is especially commendable in its conception of pathologic physiology as the essential study, morbid anatomy being a means to this end.

W. B.

Tumors of the Colon and Rectum: Their Pathology, Diagnosis and Treatment. By Jerome L. Lynch, M.D., Surgical Director, St. Bartholomew's Hospital, New York; and Joseph Felsen, M.D., Attending Pathologist, St. Bartholomew's Hospital. Pp. 242; 123 illustrations. New York: Paul B. Hoeber, Inc., 1925. Price, $12.00.

This volume, in intent, is a complete compilation of all facts concerning oncology of the large bowel and rectum. The exposition is an orderly presentation of the embryology, anatomy, physiology, pathology, cliniology, treatment (surgical and nonsurgical) and of end results. A section is devoted to the lymphatics of these structures with reference to carcinomatous extension.

The authors use their own series of cases (a considerable number) chiefly for illustration, and draw conclusions from an impressive and valuable collection of statistics. An attractive feature is a brief outline of illustrative cases with a gross and microscopic photograph of the surgical specimens.

The collaboration of clinician and pathologist on this work is a commendable arrangement, which has resulted in an unusual breadth of treatment.

W. B.

BOOKS RECEIVED.

Medical Clinics of North America. January, 1926, Tulane University Number; March, 1926, Chicago Number; and May, 1926, Chicago Number and Index Number. Philadelphia: W. B. Saunders Company, 1926.

Experimental Pharmacology. By HANS H. MEYER, and DR. R. GOTTLIEB. 2d ed. in English. Pp. 656; 89 illustrations. Philadelphia: J. B. Lippincott Company, 1926. Price, $7.00.

Modern Methods of Feeding in Infancy and Childhood. By DONALD PATERSON, B.A., M.B. (EDIN.), M.R.C.P. (LOND.), and J. FOREST SMITH, M.R.C.P. (LOND.). Pp. 106. New York: Paul B. Hoeber, Inc., 1926. Price, $3.00.

Nursery Guide. By LOUIS W. SAUER, PH.D., M.D. Pp. 206; 17 illustrations. 2d ed. St. Louis: C. V. Mosby Company, 1926. Price, $2.00.

Diathermy with Special Reference to Pneumonia. By HARRY EATON STEWART, M.D. Pp. 228; 45 illustrations and 15 charts. 2d ed. New York: Paul B. Hoeber, Inc., 1926. Price, $3.00.

Blood Chemistry. Colorimetric Methods. By WILLARD J. STONE, B.Sc., M.D. Pp. 142; 7 illustrations. 2d ed. New York: Paul B. Hoeber, Inc., 1926. Price, $3.25.

Abt's Pediatrics. VOL. VIII and Index. Edited by ISAAC A. ABT, M.D. Pp. 1102 and 249; 388 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $10 per volume.

American Relief Administration Bulletin, No. 45, April, 1926. *American Medical and Sanitary Relief in the Russian Famine,* 1921–1923. By HENRY BEEUWKES, M.D. Pp. 128; 101 illustrations.

Hay Fever and Asthma. By RAY M. BALYEAT, A.M., M.D. Pp. 198; 27 illustrations. Philadelphia: F. A. Davis Company, 1926. Price, $2.00.

Birth Control and the State. By C. P. BLACKER, M.A., M.R.C.S., L.R.C.P. Pp. 87. New York: E. P. Dutton & Co., 1926.

Treatise on Pharmacy. By CHARLES CASPARI, JR. Revised by E. F. KELLY. Seventh edition. Pp. 663; 263 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $7.00.

Psychoanalysis. By GERALDINE COSTER, B.LITT. (OXON.). Pp. 232. New York: Oxford University Press, American Branch, 1926. Price, $0.85.

The Peaks of Medical History. By CHARLES L. DANA, A.M., M.D., LL.D. Pp. 105; 56 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $3.00.

Practice of Obstetrics. By J. CLIFTON EDGAR. Revised by NORRIS W. VAUX, M.D. Sixth edition. Pp. 779; 684 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $8.00.

Elements of Pathology. By ALLER G. ELLIS, M.Sc., M.D. Pp. 544; 95 illustrations. Philadelphia: P. Blakiston's Son & Co., 1926. Price, $5.00.

Auricular Fibrillation. By J. G. EMANUEL, B.Sc., M.D., F.R.C.P. Pp. 31; 16 illustrations. Birmingham, Eng.: Cornish Brothers, Ltd., 1926.

The Principles of Anatomic Illustration before Vesalius. Pp. 58; 26 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $2.50.

The Finer Diagnoses of Acute Brain Involvements. By J. VICTOR HABERMAN, A.B., M.D., S.M.D. (BERLIN). Pp. 116. New York: *Medical Journal and Record*, 1926.

Brains of Rats and Men. By C. JUDSON HERRICK. Pp. 382; 53 illustrations. Chicago: University of Chicago Press, 1926.

Medical Clinics of North America, July, 1926. Philadelphia Number. Philadelphia: W. B. Saunders Company, 1926.

Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN, M.D., M.R.C.P. (LOND), M.R.C.S. (ENG.). Third edition. Pp. 201; 52 illustrations. New York: Paul B. Hoeber, Inc., 1926. Price, $2.50.

Clinical Pediatrics. By JOHN LOVETT MORSE, A.M., M.D. Pp. 848; 180 illustrations. Philadelphia: W. B. Saunders Company, 1926. Price, $9.00.

Politzer's Diseases of the Ear. Revised by MILTON J. BALLIN, M.D., PH.B. Sixth edition. Pp. 776; 302 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $10.00.

Research in Progress at University of Minnesota, July, 1924, to July, 1925. Compiled by CLARENCE M. JACKSON, M.S., M.D., LL.D. Pp. 306. University of Minnesota, 1926. Price, $1.25.

Epilepsy: A Functional Mental Illness; its Treatment. By R. G. ROWS, M.D., and W. E. BOND, N.R.C.S. (ENG.). Pp. 138. New York: Paul B. Hoeber, Inc., 1926. Price, $3.00.

Fundamentals of Dermatology. By ALFRED SCHALEK, M.D. Pp. 239; 54 illustrations. Philadelphia: Lea & Febiger, 1926. Price, $3.00.

Surgical Clinics of North America, June, 1926. Lahey Clinic Number, Boston. Philadelphia: W. B. Saunders Company, 1926.

Diseases of the Skin. By RICHARD L. SUTTON, M.D., LL.D., F.R.S. (EDIN.). Sixth edition. Pp. 1303; 1158 illustrations. St. Louis: C. V. Mosby Company, 1926. Price, $12.00.

United Fruit Company Medical Department 14th Annual Report, 1925. Pp. 320; illustrated.

PROGRESS

OF

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UNDER THE CHARGE OF

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Estimation of Transverse Cardiac Diameter in Man.—F. J. HODGES and J. A. EYSTER (*Arch. Int. Med.*, 1923, **37**, 707), on the basis of 80 examinations of apparently normal individuals, have worked out tables for the estimation of the normal transverse cardiac diameter in man. They state that if the heart is found to be 5 mm. wider in its greatest transverse diameter than the anticipated diameter, according to the formula, the chances are three to one that the widening is pathologic. The collection of the data and the working out of the formulæ represents a very real assistance to cardiology and should help considerably in that standards now are known for the individual who is to be examined. As the authors state, had it not been for the preparation of prediction tables for normal caloric output based on the estimation of body surface in its relation to height, weight and age, clinical calorimetry could never have become practical. The same statement might in truth be applied to the use of the Roentgen ray in abnormal conditions of the heart.

The Present Status of Our Knowledge of Pellagra.—In this Delamar lecture delivered before the School of Hygiene of Johns Hopkins University, JOSEPH GOLDBERGER (*Medicine*, 1926, **5**, 79) describes very fully the various studies which have been presented in the endeavor to show that the disease pellagra may be due to any one of a number of different causes. In the light of his own work and the experience of others he has come to the conclusion that there can be little reasonable

doubt that pellagra is caused by faulty diet. The primary dietary fault is the nature of a deficiency of a factor P–P, probably identical with the antineuritic factor. Aside from the dietary possibility of the production of this disease Goldberger lays particular stress on infectivity and devotes a considerable amount of space to the denial of an infectious agent in causing the disease. Apparently he believes that the most definite evidence that infection produces the disease has been advanced by Harris of New Orleans, who reports having infected two monkeys with a filtrate from pellagrous tissues. He dismisses this possibility by stating first that it is a question if the diagnosis was correct as it is a frequent occurrence to find in the monkey spontaneous skin eruptions similar to that described by Harris; second, that no one has been able to confirm these results with monkeys; and third, that numerous attempts to transmit this disease to the human by various methods have failed.

Arteriosclerosis and Increased Blood Pressure.—One of the interesting problems of medicine is the effect of diet on the production of arteriosclerosis and kidney disease. It may be recalled that several years ago Newburgh and Clarkson reported the production of arteriosclerosis in rabbits that had been fed a diet high in protein. This work has been looked upon with a certain amount of scepticism and it has been held that the conditions of the experiment were not rigidly controlled so that certain factors, such as infection, were not eliminated with sufficient care to remove the possibility that they may have been responsible for producing the pathological changes. Likewise it has been thought by some pathologists that the lesions that developed in these experimental rabbits were not sufficiently conclusive to say that they were the result of this specific diet. Furthermore, these reports have not been confirmed except in rabbits, guinea pigs and cats. In other animals, such as the rat, as shown by Jackson and Riggs, the feeding of the high-protein diet over many months did not produce any evidence of arteriosclerosis or chronic nephritis. Similar reports have come from other observers who have fed rats on high-protein diet. Franklin R. Nuzum, Beatrice Seegal, and Ruth Garland, with Margaret Osborne (*Arch. Int. Med.*, 1926, **37**, 733) report on a series of 48 rabbits whom they have kept on high protein for periods as long as two years. Three of the four groups were test animals and the fourth group of 12 rabbits served as controls. To the first group a liver diet was given, to the second group a grain diet, and a third group was fed soy beans. This latter is a vegetable type of protein which produces a markedly alkaline urine in contrast to the acid urines of the other two groups. The animals on the liver diet were found to have extensive arteriosclerosis, and the animals in this group showed blood pressure higher than is found in any of the other groups, and pressure was most marked in those animals with the most extensive arteriosclerosis. Albumin and casts were present in the urine, the urea nitrogen was increased, and the acidity of the urine was as high as pH 5. Seven of the 11 animals kept on a grain diet showed at autopsy marked sclerosis of the aorta and this was most extensive in those animals which had been on the grain diet for the longest time. Urine acidity and the blood pressure were not as high as on the liver diet. In the soy-bean

group none of the animals presented a true arteriosclerosis. Likewise, the kidneys gave no evidence of damage. In the control group of 12 rabbits the same findings were present. In discussion of this problem, NUZUM brings out a somewhat new consideration in explanation of the damage that occurred in the bloodvessels and kidneys of these protein-fed rabbits. Cholesterol is not thought by NUZUM to have any effect in developing arteriosclerosis. On the contrary he is of the opinion that the changes may be caused by a disturbance in the acid base balance with the excretion of very acid urine. This factor, he believes to be responsible for the high blood pressure, extensive blood vascular disease and the nephritis. Whether or not these experiments will be confirmed remains to be seen. At the present time, however, they open up a field of investigation in the problem of degenerative blood vascular disease.

Standards for the Diagnosis, Classification and Disposition of Cases of Pulmonary and Glandular Tuberculosis.—This little booklet, prepared by the National Tuberculosis Association, should be in the hands of all internists and the contents should be implanted in their brain. It is only possible with uniform standards for one medical man to understand what the other man is talking about. In order to provide such a standard, this little book offers valuable suggestions so that if it is universally followed, there will be a coördination of diagnosis, classification and disposition of patients with tuberculosis which will be of value to all concerned, patients, physicians, social workers, and nurses.

SURGERY

UNDER THE CHARGE OF

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Sympathectomy in Raynaud's Disease.—DAVIS and KANAVEL (*Surg. Gynec. and Obst.*, 1926, **42**, 729) say that the peripheral bloodvessels receive their sympathetic innervation in a segmental manner by way of the somatic nerves. Removal of the sympathetic inervation to an extremity in man is followed by hyperemia and hyperthermia, which gradually disappear within one to two weeks following operation. In certain vascular diseases of the extremities characterized by paroxysmal vasomotor symptoms and the absence of organic vessel pathology, removal of the sympathetic innervation is followed by an improvement in symptoms. Among this group are included erythromelalgia and Raynaud's disease. There are many physiological factors concerned in the control of the peripheral circulation of which the vessel musculature

and caliber are but a part. In the present state of our knowledge concerning the pathology of the group of vascular diseases known as vasomotor neuroses, we are unable to explain completely the effects produced by removal of the sympathetic innervation to the extremity.

Proliferative Gingivitis of Pregnancy.—MONASH (*Surg., Gynec. and Obst.*, 1926, **42**, 794) reports cases in which tumor-like masses were observed forming on the gums of pregnant women. They began to form at a variable time during pregnancy, increased in size unless treated and spontaneously diminished in size or disappeared completely after delivery. The growth which attracts our attention because of its size is not, as a rule, an isolated thing in these cases. It is usually accompanied by a generalized gingivitis and represents simply an exaggerated degree of this condition. The name proliferative gingivitis of pregnancy has been proposed for all phases of the condition. This type of growth is inflammatory, and should not be classed as a tumor. There is no gingivitis peculiar to and found only in pregnancy. A gingivitis practically identical with that described may be seen at times in men and women who are not pregnant. Elimination of all irritating factors and, if necessary, excision of the growth about a month or two after delivery should constitute the treatment.

Cholecystitis and Cholelithiasis.—MENTZER (*Surg., Gynec. and Obst.*, 1926, **42**, 782) writes that 66 per cent of 612 consecutive necropsy cases at the Mayo Clinic showed grossly visible pathologic changes in the gall bladder. Gall-bladder disease is essentially a disease of adults. The youngest patient was a girl, aged thirteen years. Gall stones were found in 22 per cent of the adults; 17 per cent were males, while 28 per cent were females. The youngest case occurred in a woman, aged twenty-three years. Hydrops of the gall bladder was found in 7 per cent of the cases. The inflammatory changes in the gall-bladder wall and in neighboring organs were less in cases of stones rich in cholesterin than in pigmented stones (common stones). Primary carcinoma of the gall bladder was found in 1.63 per cent of the total series, while 1 case of primary sarcoma was recorded. In 80 per cent of the cases of diseased gall bladder there was associated disease in the appendix, stomach or duodenum. Inflammatory changes in the liver are more frequent in cases of inflammatory disease in the gall bladder (gall stones) than in cases of noninflammatory disease which was termed "cholesterosis." Inflammatory changes in the pancreas are relatively infrequent in gall-bladder disease.

Hemiglossectomy by Endothermy in Carcinoma of the Tongue.—WEYETH (*Ann. Surg.*, 1926, **83**, 585) writes that by endothermy the extent of the destructive process is definitely under the control of the operator. The effect of this destruction is immediate. The operator is not obliged to wait many weeks to determine just what has been accomplished by the forces he has set in motion. There is immediate cessation from pain, because the sensory nerves are severed and capped. This capping of nerves tends to eliminate surgical shock. There is no postoperative reaction and the patient is able to return immediately to normal diet. There is no hemorrhage. No other method offers

endothermy's protection against the danger of recurrence and the threat of metastasis. The technique which isolates the malignancy before its removal as dead tissue, by a path of protective destruction drawn in healthy tissue and which thereby seals lymphatics, to and from the affected part, is peculiar to endothermy.

Dermoid Cysts of the Mediastinum.—BEYE (*Ann. Surg.*, 1926, **83**, 577) states that dermoid cysts of the mediastinum are rare tumors. Patients suffering from such tumors may be cured or relieved by operation. The symptom complex is quite variable. Symptoms may be due to pressure of the enlarging mass upon the adjacent tissues or organs, or may be due to irritation of the tumor producing the clinical picture of an intrathoracic inflammatory process. The tumor is commonly in close contact with the large vessels in the upper mediastinum and often adherent to them. It may be more or less densely adherent also to lung, pericardium, sternum, chest wall or diaphragm. Exploratory thoracotomy is indicated when the diagnosis of a mediastinal dermoid is suspected.

Use of Iodized Oil in Roentgen Ray Diagnosis of Spinal Lesions.—SCHMIDT (*Am. J. Roentgenol. and Rad. Therap.*, 1926, **15**, 431) states that the diagnostic importance of iodized oil in the Roentgen ray diagnosis of spinal lesions has been definitely established. The method is of special value in the diagnosis and exact localization of tumors of the spinal canal. As demonstrated in our series of examinations, injections of iodized oil into the spinal theca may further give valuable information in other neurologic conditions, for example, multiple sclerosis, spine injuries, and so forth, although the results are not constant and our present state of experience often does not permit definite conclusions. The dangers and disadvantages of the method should not be disregarded apart from the direct danger of a medullary lesion by faulty technique, the intraspinal injection of iodized oil constantly produces a transitory aseptic meningitis with more or less severe local and systemic symptoms. Late sequelæ may result from irritation ("foreign-body action") by the extremely slowly absorbable oil.

PEDIATRICS

UNDER THE CHARGE OF

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Asthma in Children.—PESHKIN (*Am. J. Dis. Child.*, 1926, **31**, 763) in this paper considers the subject from the standpoint of etiology. He studied 100 consecutive cases of asthma in children who were tested in routine manner with 97 food, epidermal, pollen, bacterial and dust proteins by the cutaneous scratch method. These were observed for a period of from one to four years. He feels that the futility of employing inactive substances for the skin tests cannot be overempha-

sized. All reactions above the control are definite positive reactions to the scratch tests. He has demonstrated the importance clinically of the ± reaction. He subdivides asthma into three main groups, with the following frequency of occurrence: (1) Protein sensitive, 79 per cent; (2) nonprotein sensitive, 18 per cent; (3) para-asthma, which is a new term, 3 per cent. The most common age of onset of asthma in the protein-sensitive group was two years. Onset of asthma did not occur after ten years of age. The most common onset in the nonprotein sensitive group seems to be around one year and after that it is fairly evenly distributed up to the ninth year, after which no cases occur. The age of onset in the para-asthma group is prior to eighteen months. Ninety-eight per cent of the patients of the protein-sensitive group reacted to the inhalants. The most common of these in the order of frequency were rabbit hair, house dust, duck feathers, horse dander, cat hair and ragweed. Sensitization to rabbit hair occurred in 49 per cent of all of the asthmatic children and in 62 per cent of the protein-sensitive group. Those who exhibited a positive skin reaction to rabbit hair were classified into five groups, according to the role that this sensitization played in the etiology. The most common primary sources of exposure were from pillows and mattresses. It may be allowed that house dust is responsible for more skin reactions than any other substance, but as an etiologic factor in asthma it does not assume the importance of rabbit hair. Duck and goose feather sensitizations are common while chicken feather sensitization is relatively uncommon in this class of children. One-half of the children of the protein-sensitive group reacted to horse dander. As a cause of sensitization this accounts for only 10 per cent of these cases, and it was not the sole etiologic factor in any case. Positive skin reactions to rabbit hair and horse dander in the same individual occurred in 43 per cent of the patients of the protein-sensitive group. As an etiologic factor asthma occurred three times more frequently with rabbit hair than it did with horse dander in these patients. Sensitization to cat hair occurred in 24 per cent of the entire series, or in 31 per cent of the protein-sensitive group. It was a frequent contributory etiologic sensitization only. Twenty-five per cent of the protein-sensitive group gave positive skin or conjunctival pollen reaction. Pollen was an etiologic factor in about one-half of these cases, and of these ragweed was the most common. One-third of the cases with a pollen etiology were refractory to the cutaneous but positive to the conjunctival test. Children with asthma having an etiologic pollen sensitization invariably show their protein etiologic sensitizations. The author cites 2 cases in which a pollen history and the cutaneous reactions against pollen were negative when first tested, but after two years both children acquired hay fever, and then for the first time showed positive cutaneous reactions to pollens. A reliable diagnosis of bacterial asthma cannot be made at present with materials that are obtainable and by the methods which are employed. Seventy-one per cent of the patients of the protein-sensitive group gave positive food reactions. Food sensitization in asthmatic children usually takes place prior to the seventh year. The most common age of the onset of asthma was two years. The phenomenon of natural desensitization generally occurs after the eighth year. Radish, coffee, wheat, barley and lettuce are the com-

monest food reactions encountered in these children, but fish, egg and nut are directly responsible for most symptoms attributable to food intolerance. Cows' milk usually causes trouble in late infancy and early childhood. Mustard and radish sensitizations appear to have something biologically in common. Nine per cent of the protein-sensitive cases or one-eighth of the cases giving food reactions do so by reacting to entire food groups, such as fish or meat or both. This is of diagnostic significance. Food plays an extremely valuable role in the production of allergic symptoms in children, and does not attain the importance of the inhalant proteins. Skin tests with horse serum should be performed in every case of bronchial asthma before the use of therapeutic serums is attempted. Drug intolerance has not been observed in these children. Positive protein skin reactions were found in 10 per cent of the children with asthma in whom there was no etiologic connection. This is exactly the incidence of reaction occurring in normal children.

Splenic Diseases with Special Reference to Splenectomy in Children.—KUHN (*Arch. Pediat.*, 1926, **43**, 407) states that the spleen, although its function may not even at the present time be fully understood, may best be considered as a filter placed in the blood stream under normal conditions to filter the red blood cells which disintegrate daily. The spleen has very aptly been called "the graveyard of the red blood corpuscles." Under pathologic conditions cells foreign to the circulation, such as nucleated red blood cells, myelocytes, bacteria and other toxic agents are also filtered out, the retention of which adds greatly to the increase in the size of the organ. Generally speaking, splenectomy is contraindicated in the leukemias and pernicious anemia. In Gaucher's disease and von Jaksch's anemia the removal of the spleen should be undertaken only after the greatest deliberation. In many cases of Banti's disease, congenital family hemolytic jaundice and purpura hemorrhagica splenectomy is definitely indicated. It is firmly recognized that the spleen is not necessary to life, and improvement in surgical technique has transferred the treatment of many of its diseases from the internist to the surgeon.

Acute Alimentary Disturbances in Infants.—MITCHELL (*Indiana State Med. Assn. J.*, 1926, **19**, 135) made a clinical study of 35 children and also analyzed observations of others, and he feels convinced that in infants who gave clinical evidence of dehydration the determination of the blood-urea nitrogen, uric acid and carbon dioxid of the blood plasma showed definite values, depending on whether or not the infants were suffering from toxic symptoms and hyperpnea. If no toxic symptoms were noted the blood nonprotein-nitrogen constituents were practically normal. In the presence of moderate toxic symptoms there usually was noted a moderate increase of nonprotein constit uents, but if the patient showed distinct evidence of toxic symptoms the blood-urea nitrogen and uric acid usually were decidedly increased over normal, although the increase was neither consistent nor great enough to indicate that uremia was a primary cause of the fatal termination. A decrease in the carbon-dioxid capacity of the blood plasma was

found when the dehydrated infants showed clinical evidence of hyperpnea. In other infants in whom hyperpnea was not noticeable, but who were moderately toxic and whose blood usually showed an increase in nonprotein-nitrogen constituents, the plasma showed a diminished carbon-dioxid capacity in some cases. Usually the carbon-dioxid capacity of the plasma was normal, when there was no increase in the respiratory rate and depth. The alkali reserve was usually greatly diminished before death. This did not occur in several infants and in several with equally low alkali reserve recovery followed, so that it would seem that acidosis is an accompanying phenomenon and not a primary cause either of the condition or of its fatal termination.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Hypercholesterolemia.—WEIDMAN and SUNDERMAN (*Arch. Dermat. and Syph.*, 1925, **12**, 679 and 840) have studied the duration, extent and methods of inducing experimental hypercholesterolemia, and give a comprehensive consideration of the normal figures and the comparative amounts of blood cholesterol in man and laboratory animals. Their review of the various techniques of estimating the blood cholesterol for man and the lower animals indicates that the values differ markedly by the several methods. They, accordingly, ran normal controls on 4 men, 3 monkeys, 4 dogs, 3 cats, 4 rabbits and 3 guinea pigs, using the Myers-Wardell method as modified by Oser and Karr. Each animal was tested on at least four and sometimes five different occasions. Their result for the lower animals were: Rabbits, 62 to 80 mg. per 100 cc. of whole blood in each case; guinea pigs, 81 to 88 mg.; cats, 94 to 100 mg.; dogs, 111 to 118 mg.; monkeys, 121 to 136 mg. The animals were kept under uniform dietary and environmental conditions for weeks previous to the tests, and the blood samples were taken before the morning feeding. For man, the authors found 140 to 160 mg., but they are inclined to think that the correct value probably lies between 160 to 180 mg., as Luden believes. A more perfect method of extraction may decidedly change this opinion. The absolute values are not vital, because the essential point in any given case is whether it is greater or less than the standard which is accepted as normal. Of the various avenues for introducing cholesterol to produce experimental hypercholesterolemia in animals the intraperitoneal was chosen to insure a more lasting effect, using 0.5 gm. sterilized crystals of a

chemically pure product. Various common laboratory animals were used and the determinations were made at weekly intervals. The authors found that the rabbit is the most susceptible to experimental cholesterolemia, the effect lasting up to six weeks after an intraperitoneal injection. On oral feeding, rabbits will have a hypercholesterolemia with almost any substance rich in cholesterol, but the intraperitoneal method gives a more constant sustained blood cholesterol value.

Intramuscular Absorption of Some Insoluble Bismuth Compounds as Revealed by the Roentgen Ray.—Cole, Farmer and Miskdjian (*Arch. Dermat. and Syph.*, 1926, **13**, 219) used the Roentgen ray to follow the rate of absorption of deep injection into the lumbar muscles of various bismuth salts, using the following: Metallic bismuth, bismuth oleate, bismuth oxybenzoate, bismuth salicylate and potassium bismuth tartrate. Their findings indicated that injections of metallic bismuth are dangerous, and if persisted in will lead to cumulative absorption and possibly even to fatal results. The same is probably true, although to a lesser extent, of bismuth oleate. Bismuth salicylate likewise is open to the same criticism, and it should be replaced by one of the more soluble bismuth salts—perhaps the potassium bismuth tartrate preparations. These salts, especially if injected intragluteally only once a week, are less likely to give rise to cumulative action. The patient should, however, be closely watched, as even this salt is not above criticism as far as its absorption is concerned. The authors doubt the wisdom of injecting insoluble bismuth salts twice weekly, for only a small amount of the salt will be absorbed in the time allowed.

Epilation in Mice as a Biologic Standard for Determining Roentgen Ray Dosage.—Hazen and Milstead (*Arch. Dermat. and Syph.*, 1926, **13**, 230) found the epilation dose for removing the hair from the backs of young male mice with the Roentgen ray to be just six times that of man. Complete epilation occurs in three weeks. The factors used include focal skin distance, 9 inches (milliampèrage, 4); spark gap, 7½ inches (sharp points); no filter. An interesting observation was a secondary effect at the original site (near root of the tail) following an epilation dose between the shoulders. It occurred long before the hair fell in the newly irradiated area. The epilation dose of radium was found to be twice that in man, but the experiments were conducted with radium in needle form (20 mg. in the form of 5 mg. needles). Mice were chosen for these experiments because they were the most available animals. The authors feel they have established a biologic standard by which one may control practical technique and one which adds safety and accuracy to superficial Roentgen ray therapy.

The Routine Management of Syphilis in St. Thomas' Hospital.—Several noteworthy additions and suggestions on the technique of treating syphilis are made by Harrison (*Brit. J. Venereal Dis.*, 1926, **2**, 19). Before each arsphenamin injection the patient is given the following drink: Glucose, 14 drams; sodium bicarbonate, 15 grains; oil of lemon, 1 minim; water, to make 3 ounces—in hope that the liver cells will take up glycogen and have less affinity for the arsphenamin, which is a liver poison and may cause jaundice. For the same

reason patients are not encouraged to abstain from food for hours before the injection, as is often recommended. Two hours' abstinence seems to be sufficient preparation for an intravenous injection, and no abstinence is required at all before a subcutaneous. Bismuth or mercury is usually administered at the same time as arsphenamin, partly for the sake of convenience, but chiefly because the author believes that the two act better when given simultaneously than when they are given in separate courses. This belief is supported by animal experiments by Lehnoff-Wyld, which indicated that the action of arsphenamin is intensified when another metal is present in the circulation at the same time. Cerebral symptoms with epileptiform convulsions, occurring as a toxic effect of arsphenamin should be treated by lumbar puncture, drawing off 20 to 30 cc. of spinal fluid. In addition, the patient should be bled a pint and have an injection of adrenalin chlorid (1 cc. of $\frac{1}{1000}$ solution diluted with 5 cc. physiologic saline given slowly, intramuscularly).

Treatment of Neurosyphilis by Malaria: A Preliminary Report.—O'Leary, Goeckerman and Parker (*Arch. Dermat. and Syph.*, 1926, **13**, 301) report their preliminary observations after a ten months' trial in a series of 35 patients with neurosyphilis who were inoculated with malaria plasmodia. Many of the patients of this group had been treated with tryparsamid, some with benefit and others without. Of the 24 patients with frank paresis, 25 per cent showed complete remission that allowed them to return to their former occupations within two months after the malaria was stopped. Thirty-seven per cent were definitely improved in one way or another and 2 died, 1 as a result of the malaria and the other six months later in convulsions. Thus far in this series the "fever therapy" has had practically no effect on optic atrophy, gastric crises, persistent lightning pains with negative serologic findings, asymptomatic neurosyphilis and paresis sine paresi. The mental and physical symptoms are most favorably influenced by the treatment, few changes being observed in the objective findings. There had been no serologic changes in the blood or spinal fluid up to the time of reporting. The use of arsphenamin, mercury or tryparsamid immediately after the malaria was attended with definite evidence of relapse from remission. The majority of the complications noted were transient and disappeared with cure of the malaria, although complications attributable directly to the syphilis may cause some embarrassment. Myocarditis, nephritis, marked weakness or wild delirium may demand the cessation of treatment. A rise of blood urea above 100 mg. per 100 cc. is an indication for terminating the course with quinin.

A New Application for Varicose Ulcers.—Davis (*Arch. Dermat. and Syph.*, 1926, **13**, 519) has used a new solution with marked success on varicose and indolent traumatic ulcers. The formula was proposed by F. P. Dunnington; it consists of boracic acid, 63 gm.; potassium hydroxid (stick), 28 gm.; water, 200 cc. It is prepared by heating the boracic acid and potassium hydroxid with 150 cc. of water in a porcelain dish. This is allowed to cool and is filled to 200 cc., giving a solution of specific gravity of 1.2. The full strength frequently is quite painful

on ulcers, but the pain is usually of short duration. Patients must be warned that the preparation will remove the varnish or paint from furniture. The usual routine is to mop on the solution in half strength after the base of the ulcer is cleaned. About ten minutes later Lassar's paste is applied on strips of muslin, the salve being reapplied twice daily. In a series of 55 cases gratifying results were obtained in most patients who persisted in treatment; some disappeared before permanent results could be obtained, but flat failure to respond to treatment occurred in only 1 case. All cases were ambulatory except 1, and many were of long standing. It appears to be best to begin treatment by using the solution one-half strength, increasing to full strength if the pain is not too great. It should be applied at least three times a week.

OBSTETRICS

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Puerperal Fever. II. Streptococcus Hemolyticus Toxin and Antitoxin.—ABRAHAM LASH, M.D., and BERTHA KAPLAN, M.S. (*J. Am. Med. Assn.*, 1926, **86**, 1197). In a previous report (*J. Am. Med. Assn.*, June, 1925) the authors reported the presence of a toxic substance in the Berkefeld V filtrate of broth cultures of Streptococcus hemolyticus isolated from the blood of patients with puerperal fever. Intracutaneous injections of the filtrate (sterile) produced inflammatory reactions, varying in degree and incidence with the dilution of the filtrate and the presumable immunity of the patient. There was a definite latent period between injections and reactions. The present experiments were to determine further characteristics of a toxin and the specificity of the organism. Heating a 1 to 100 dilution of the filtrate in a water bath at 70° C. for fifteen minutes and another quantity at 90° C. for sixty minutes gave negative intercutaneous reactions in pregnant women known to be strongly positive to a 1 to 1000 solution. The negative tests were due to the destruction of the toxic substance in the filtrate by heat. An immune serum was prepared by repeated intracutaneous injections, of the undiluted filtrate into a rabbit, 25 injections were given at intervals of three days. A control serum was obtained from a nonimmunized rabbit. Ten pregnant women at term who gave a positive test with the 1 to 1000 dilution of the filtrate were tested with varying dilutions of the filtrate mixed with immune serum and with control serum. In the control tests strongly positive reactions occurred.

Therefore, the toxic substances in the filtrate were neutralized by the immune serum. Results of the precipitin tests demonstrated a nonspecificity of the strains of Streptococcus hemolyticus isolated from puerperal fever, yet they indicated a relationship between these strains. The lethal dose in a rabbit of the puerperal strain suspended in physiologic sodium chlorid solution was determined. Another rabbit was immunized with the undiluted toxin produced by the organisms isolated from this rabbit and then given a lethal dose intravenously. The animal was not affected and when killed one month later showed no pathologic changes. The authors concluded that this toxic substance is a toxin because: 1. There is a latent period between injection and reaction. 2. The toxic substance is heat labile. 3. It is neutralized by immune serum and not by nonimmune serum. 4. The precipitin tests further show the development of immune bodies by the toxin. 5. The repeated injections of the toxin produced sufficient antitoxin to protect rabbits against the lethal dose of the puerperal Streptococcus hemolyticus.

Mortality in Obstetrics.—Editorial. (*Atlantic Med. J.* 1926, **24**, 473.) A recent insurance company bulletin states that among policy holders there has been very slight improvement in the maternal mortality during the last fourteen years in contrast with the very marked betterment in so many other diseases. Among white women, aged fifteen to forty-four years it runs second to tuberculosis as the cause of death. This study is based on a review of 400,000 white women policy holders. The "accidents of pregnancy," abortions, miscarriages, ectopic gestations, and so on, have shown a slightly upward trend and the accidents of labor, malpresentations, difficult labor, Cesarian sections and other operative interferences, a more pronounced rising tendency. There is a marked decline in puerperal sepsis and an improvement in the death rate from eclampsia, evidently due to prenatal care. The infant mortality shows a marked decrease.

The Cautery Treatment of Chronic Endocervicitis.—Chronic endocervicitis with or without erosion and the treatment instituted is clearly set forth and comprehensively considered. Carl Henry Davis (*J. Am. Med. Assn.*, 1926, **86**, 1763) refers to the work of McGrath, Winter, Curtis and Moench and comes to the conclusion that the cervical irritation of chronic character is to be looked upon as of serious moment. That the early differential diagnosis between early carcinoma and chronic endocervicitis may be impossible without a microscopic examination. He emphasizes the fact that every woman patient who complains of pelvic symptoms should have a speculum examination. That endocervicitis is frequently a factor in dysmenorrhea, sterility, backache, nervousness and general debility. When present it should be cured as part of medical treatment. The technique of treatment for office use is comprehensively set forth. That this treatment can be looked upon as curative and in some cases but not as a cure-all. It is a prophylactic measure and may prevent more serious disease of the cervix in the future. He warns against using the cautery during the acute stage of cervical infection and in those cases with retroflexion, the uterus should be replaced before treatment is instituted. Syphilis

of the cervix contraindicates the cautery. Douches in these cases are of questionable value and he warns against the excessive bleeding which may be produced, following this treatment.

Puerperal Fever.—ABRAHAM F. LASH (*J. Am. Med. Assn.*, 1926, **86**, 1427) deals with the production of the toxin in Streptococcus hemolyticus isolated from the blood of patients with puerperal fever. A comparison of the toxin with the Streptococcus hemolyticus of scarlet fever by means of the skin reaction has been tabulated in a series of 247 women.

Spontaneous Rupture of the Uterus in Labor following Sturmdorf Tracheloplasty.—NICHOLSON J. EASTMAN (*Am. J. Obst. and Gynec.*, 1926, **11**, 500). A full case report with references to the literature shows that dystocia can easily follow the operation of tracheloplasty and trachelorrhaphy. As far as the author is aware this is the only reported spontaneous rupture of the uterus subsequent to a Sturmdorf tracheloplasty.

Report of Case of True Ovarian Pregnancy.—JAMES R. MANLEY (*Am. J. Obst. and Gynec.*, 1926, **11**, 512). A primary ovarian pregnancy is the result of fecundation of the ovum while still within the Graafian follicle. Certain conditions must be fulfilled to prove a case of primary true ovarian pregnancy. The tube on the infected side must be intact. The fetal sac must occupy the position of the ovary. The pregnancy must be connected to the uterus by the utero-ovarian ligament. Ovarian tissue must be formed in several portions of the wall and that the embryo itself must be found is probably not essential.

Midwife Work in Pennsylvania.—MARY RIGGS NOBLE (*The Atlantic Med. J.*, 1926, **29**, 625). This article shows clearly the condition that surrounds this work of the midwives in Pennsylvania. It deals with the registration and supervision of the midwives in certain locations and in groups where the foreign population is the dominant factor. Operating in coöperation in this survey has been slow in results and supervision and instructions have been difficult with only one full-time woman physician for the supervision and instruction which has made the work necessarily slowly productive, yet of great benefit. This article deals with the registration of births including the illegitimates, the regulation requiring the midwives to have in their possession a certain amount of apparatus, and the insistence in the care of the eyes of the newborn. The work was begun in June, 1922, since that time the tables included in the article show clearly the population of the counties, the number of midwives, the maternal deaths, stillborn cases and the reported number of deliveries, and the percentage mortality of cases coming under the care of the midwives.

GYNECOLOGY

UNDER THE CHARGE OF

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Vulvovaginitis in Children.—The disease known as vulvovaginitis in children is of interest alike to the pediatrist and gynecologist, and although it has received many types of treatment at the hands of both of these classes of men it remains today as a condition which is very refractory to all treatment. Although for many years this condition was considered to be of gonorrheal origin in all cases, at present the discharge in many of these little children is believed to be due to other types of infection. In expressing his views upon this interesting subject WILLIAMS (*Am. J. Obstet. and Gynec.*, 1926, **11**, 487) states that the term vulvovaginitis is neither accurate nor sufficiently descriptive for in the mild cases of vulvovaginitis the vagina is rarely, at least, markedly involved. He believes that there is considerable doubt that a large percentage of the cases are caused by the gonococcus. Many outbreaks, especially of the epidemic type in babies' homes, schools and hospitals, are caused by the ordinary mucous membrane infecting organisms responsible for colds and upper respiratory infections. Masturbation prompted by mechanical irritation of undisturbed secretion about the labia and clitoris causes a certain percentage, and a flagrant disregard of cleanliness is the basic cause in many others. Contamination from the rectum to the delicate tissues anterior must be considered. Weakened resistance in poorly-nourished or ill-cared for children in the lower grades of society heightens the susceptibility to infection of the genital organs. Dissemination at times arises in birth infections, communal towels, toilets, baths and thermometers. During the first twenty-four hours of life the vagina is said to be sterile, but by the third day it contains microörganisms. These include the various staphylococci, streptococci; later on the Bacillus coli has been found, and in older children intestinal bacteria form about half the organisms present in the vagina. The finding of organisms so constantly in the vaginas of young children might negative the existence of a natural antiseptic function at this age. The vaginal bacillus of Doederlein is said not to appear until puberty; thus the vaginal canal in infancy does not have its later natural protective function. As a general statement the prognosis of infantile vulvovaginitis is regarded as favorable. The duration of the disease should be relatively short, provided that the causative factor is not continuously active or that the greater irritation of too active treatment is not responsible for the continuance of the disease. The basic principle in treatment is cleanliness, ordinary soap and water cleanliness. This in itself will effect a cure in a large propor-

tion of the simple catarrhal, mechanically-produced types resulting from dirt irritations, and nonspecific bacterial cases. Combined with such simple hygienic therapy may be added soothing dusting powders. In some instances tonic treatment may be added. In cases of oxyuriasis the proper helminthic must be added. In the specific cases, or in the nonspecific cases resisting treatment, local antiseptic measures are in vogue. The medicaments used are many. The various silver salts, especially the colloidal silver preparations, various dyes and other chemicals have been advocated for use locally by applications, irrigations, douches or by suppositories or bougies, and by injection in pastes or ointments. The difficulty of treating easily terrified young children makes the actual carrying out of almost any form of treatment not an easy matter. If the condition resists simple hygienic therapy or the locally applied chemicals, vaccines should be tried.

Irradiation of Cervical Cancer.—On previous occasions we have called attention to the work that is being done in the treatment of cancer of the cervix at the Woman's Hospital in New York City, and at this time we again quote from a recent article by WARD and FARRAR (*Am. J. Obst. and Gynec.*, 1926, **11**, 439) who are able to show 23.6 per cent of their cases of all kinds alive over five years, whereas, their results in the cases in which the disease had not extended beyond the cervix showed 52.9 per cent alive over five years. As a result of their careful study of this subject, they are of the opinion that for purposes of comparative study a standardized simple classification of the extent of the disease, and the same rules of estimating end results and percentages, should be adopted by all clinics. A monthly follow-up conducted in person by the surgeon in charge of the patient is of inestimable value as a factor in the successful treatment. The details of technique are important. Especially should overradiation be avoided, and subsequent treatment should be based upon the reaction to the test dose of radium. This does not permit of employing repeated doses at short intervals, regardless of the response to the *first* dose of radium. In their experience repeated irradiations, three or more, have been of distinct value in certain advanced cases. By watchful waiting it is often possible to extinguish the fire that is rekindling, before it has gained much headway. According to their results, radium alone is preferable to surgery in all classes of carcinoma of the cervix. As at least 50 per cent of the early cases of carcinoma of the cervix can be saved by radium, the importance of educating the laity and the family physician to seek an early diagnosis is imperative. While carcinoma of the fundus is best treated by surgery, many times the operative risk is poor and resort must be had to radium and Roentgen ray therapy. Large amounts of radium are not necessary to produce satisfactory results. The value of Roentgen ray therapy in carcinoma of the uterus is still an undetermined question. Every case of carcinoma of the uterus should be individualized and treated accordingly.

RADIOLOGY

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Pyelitis in Pregnancy.—Study of the urinary tract by the injection method is more accurate than urinalysis for determining the presence of disease in the urinary tract because it not only demonstrates the presence of pathology but often shows the anatomic extent of the lesion. BUTLER (*Am. J. Roentgenol. and Rad. Ther.*, 1926, **15**, 144) thinks the injection method is particularly adaptable to cases of pyelitis in pregnancy for in these the treatment consists of drainage and lavage and the diagnostic study can be carried on simultaneously with the treatment. Two years routine use of this method has brought out many interesting and instructive facts. The infecting agent has been colon bacillus most frequently; the condition has been more frequent in multipara; may occur early or late in pregnancy; affects usually the right side (80 per cent in this series), probably due to intimate association of the lymph channels of the cecum and ascending colon and kidney and ureter. The author recognizes three types anatomically: (1) Simple dilatation of the ureter and renal pelvis with or without kinks in the ureter; (2) dilatation of the renal pelvis with blunting of the calyces from continued infection and increased pressure, and (3) real destruction of the kidney substances. In the discussion Williams described two types: (1) The lighting up of an old inflammatory process, and (2) acute primary pyelitis of pregnancy and continued that dilatation of the kidney pelvis is very frequent during the latter months of pregnancy without infection.

Tuberculosis of the Sacroiliac Joint.—Remarking the paucity of information on this subject in the literature MCCULLOUGH (*Am. J. Roentgenol. and Rad. Ther.*, 1926, **15**, 150) concludes that the condition is uncommon, most frequent in young adults and extremely rare in children. Goldthwait and Osgoode, in 1905, and Albee, in 1909, contributed studies in the anatomic structure and pathologic conditions involving this joint. Tuberculosis produces the same changes in the sacroiliac as in other joints. The disease begins in the sacrum more frequently, to which it may have extended from a focus in the lumbosacral joint or it may involve the ilium. Bone destruction occurring with secondary extension to the joint may be arrested at an early stage with resultant obliteration of the joint. More often there is destruction of the joint surfaces with perforation of the capsule and abscess formation. The perforation occurs usually anteriorly into the pelvis, the abscess may extend upward into the gluteal region along the posterior aspect of the joint, may point in the groin or ischiorectal fossa or rupture into

the rectum. Pain is usually unilateral, aggravated by motion and relieved by postural change. Lateral compression of the pelvis produces pain in the affected side. Tenderness on direct pressure over the joint and absence of pain on pressure over the nerve course differentiates it from sciatic neuritis. Limitation of motion is marked with patient standing; flexion of the hips with fixation of the lumbar spine is characteristic in the supine position. Raising of the leg with the knee joint extended is definitely limited; further flexion of the thigh causes pain, referred to sacral region or legs (Goldthwait sign). Peculiar attitudes in sitting, standing and walking, inclination of the body toward the sound joint, standing with the weight on the unaffected leg, short stepping when walking and dragging of the affected leg while climbing steps with a feeling of insecurity of the back are all suggestive. Differentiation can largely be made by roentgenologic examination.

PATHOLOGY AND BACTERIOLOGY

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The Bacteriology of Subacute Infective Endocarditis.—WRIGHT (*J. Path. and Bacteriol.*, 1925, **28**, 541) paid particular attention to the technique of blood culture. He found that media which contain trypsin or sodium citrate are slightly superior to those which do not, and that media so employed will permit the growth of organisms if they are present even in such small numbers as 1 or 2 per cubic centimeter. Failure to isolate a streptococcus from the blood indicates the absence of such organisms from the specimen examined. The concentration of sodium citrate in a medium should not exceed 0.2 per cent. Delay in inoculation of media with infected blood was found to have no effect on the organisms in the blood if it was kept at room temperature. Delay in growth in blood cultures from cases of subacute infective endocarditis he found to be due largely to prolongation of the latent period and that this phenomenon appeared to depend upon certain peculiarities of the organisms rather than upon inhibitory factors in the blood. He points out as an error in blood cultures taken shortly before death and postmortem, the fact that streptococci are the commonest organisms found in the heart blood after death from causes other than subacute infective endocarditis, and that furthermore terminal invasion of the blood stream by pyogenic organisms in cases of subacute infective endocarditis can frequently be demonstrated. Therefore culture made during life should be repeated confirmed and if possible antibody for-

mation should be demonstrated. Cultures made from the vegetations are significant only if the possibility of terminal infection has been ruled out, that is, if the heart blood is sterile. In his own series of 19 cases 12, or 63 per cent, showed a septicemia with nonhemolytic streptococci. The blood of these cases contained antibodies, and he considered the septicemia to be due to the escape of organisms from the lesions in the valves. Certain cases showed no septicemia, and examination of the valvular lesion showed what appeared to be disintegrating organisms. Bacteria were easily demonstrated in the vegetation of the septicemia cases.

On Liver Necrosis and Cirrhosis Produced Experimentally by Coal Tar.—During experiments on the production of cancer by applying coal tar to a rabbit's ears, DAVIDSON (*J. Path. and Bacteriol.*, 1925, **28**, 621) found that in several animals cirrhosis of the liver had supervened. This was further investigated by carefully selecting rabbits free from coccidiosis and other infections and applying to their ears coal tar at intervals from a few days to a month. Some were given subcutaneous injections of a solution of coal tar in ether. All animals showed a progressive loss of weight and a series of liver necrosis varying from acute, subacute to chronic could be produced. The acute changes were similar to those found in acute yellow atrophy in the human subject. The chronic changes, including regeneration of the liver, closely resembled those of typical atrophic cirrhosis. The arrangement of the cells in the regenerated tissue was irregular, and in some instances adenomatous growth occurred. It is suggested that the changes observed in acute yellow atrophy, subacute yellow atrophy and atrophic cirrhosis of the liver are different stages in one process.

Tuberculosis in the Tropics.—In a review of 402 autopsies conducted in São Paulo, southern Brazil, LAMBERT and FILHO (*Am. Rev. Tuberc.*, 1925, **12**, 173) contrast the tuberculous conditions found in this subtropical area with those in the temperate zone. Their cases group themselves under: "Lethal," those dying of the disease, 20.6 per cent; "subsidiary," those with active tuberculosis with another cause of death, 15.4 per cent; "healed," 4.5 per cent; "doubtful," 32.3 per cent; this gives an aggregate of 60 per cent which showed definite tuberculous involvement, where only half the "doubtfuls" are included. The importance of this disease in the mortality figures is doubtless exaggerated in this report, as the subjects of autopsy belonged to the drifters. Contrasting with the findings in North America, the pathologic response was exudative rather than proliferative; also the incidence of the bovine type was exceedingly low, and this is doubtless to be ascribed to the custom of boiling all milk used. It was found that blood infections can occur with healing, as scars were found scattered through the organs. The involvements of trachea, intestines and meninges were associated with the lethal group. The fact of the higher percentage of lethal cases among the negroes and the predominance of healed among the whites points to the former group as a "non-immunized" race though "tuberculized" for several generations.

HYGIENE AND PUBLIC HEALTH

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The Legal Authority and Limitations Governing Federal Public Health Activities.—KERR's (*Pub. Health Repts.*, 1925, **40**, 1677) discussion of the subject may be illustrated by the following extracts of salient features: "The Federal Government undoubtedly has potential as well as active powers, the former of which may not be exercised as long as the States individually exercise them. The jurisdiction of the Federal Government in public health matters extends over foreign intercourse, interstate intercourse, Federal Territory and administrative affairs, including protection of the Indian tribes. As examples of these fields of activity and the methods of covering them, the District of Columbia may be cited as a strictly Federal Territory wherein local health matters are specially legislated for by Congress." . . . "In matters of health relating to international and interstate intercourse, the United States Public Health Service is the agency depended upon. It operates through its own department—the Treasury—or in coöperation with other departments having to do with factors other than health affecting international or interstate commerce. In the broad sense any law or measure having for its object the promotion of prosperity, and the general welfare has a bearing on health. As examples, may be mentioned the compilation of the decennial census and the control of the purity of foods and drugs. But both are essentially economic measures." . . . "One of the first Federal laws relating to the public health was enacted, May 27, 1796. It authorized the President to direct the revenue officers and revenue cutters to aid in the execution of maritime quarantine and in the execution of the health laws of the States. Two years later a law for the relief of sick and disabled seamen was enacted." . . .

"RELIEF OF THE SICK AND DISABLED. All organized measures for the relief of the sick and disabled have some public health bearing, but the law of 1798 above mentioned has special significance because it was the first one enacted to safeguard the lives and health of any industrial group. Under its provisions any American seaman taken sick or injured while following his calling is entitled to relief in hospitals and dispensaries of the service." . . . "An act of September 7, 1916, of even greater importance, authorized medical and hospital services to any employee of the Government injured in the performance of his duty. By judicial interpretation the occupational diseases are injuries within the meaning of this law." . . . "These measures in the interest of governmental employees are the nearest approach to official sickness insurance in this country. Supplemental

laws will in all probability be enacted in time to require physical examinations of all Government employees before entrance on duty in the interest of efficiency. Even now these examinations are performed, but not by Government medical examiners."

"SANITARY SUPERVISION OF INTERNATIONAL TRAFFIC. The Federal health laws as enacted from time to time are the direct results of repeated epidemics. On account of smallpox, vaccine virus was introduced voluntarily by an officer of the service in 1807. In 1813 a law was passed to encourage vaccination by providing for the distribution of vaccine virus. The first permanent quarantine law, enacted April 29, 1878, followed a severe and widespread epidemic of the previous year. The passage of the law of February 15, 1893, was intimately associated with the cholera outbreak in Europe in 1892, and the quarantine act of June 19, 1906, followed the epidemic of yellow fever in the Southern States in 1905. Under these and a few minor laws the national system of maritime quarantine was developed. A peculiar feature of this system is that existing regulations automatically become operative on the occurrence of epidemics in foreign ports, thus obviating the necessity for the promulgation of quarantine against a particular port." . . . "Of equal importance from the standpoint of the prevention of the introduction of exotic diseases in the inspection of arriving aliens. A long series of immigration laws has been enacted during the period March 3, 1891, to February 5, 1917. The medical inspections under these laws by the Public Health Service is a Federal function, the object being to prevent the introduction of exotic diseases and to exclude the mentally unfit who will endow their offspring with an unstable mentality." . . .

"SUPERVISION OF SANITATION IN RELATION TO INTERSTATE TRAFFIC. While Federal powers in respect to traffic between the several States of the Union are far reaching, these in large part have been potential. The equity of our form of government predicates as full autonomy as possible of all its component parts. By reason of the fact that the exercise of sanitary police powers over matters within the States devolves on their authorities, it is only when these matters affect other States that they come within the jurisdiction of the Federal Government. Even then the health authorities of the several States are relied upon, and it is only when they fail or refuse to take necessary measures to prevent the spread of infectious diseases that the Federal Government may exercise its superior authority." . . . "In order to be in position to combat the spread of cholera yellow fever, smallpox. plague, typhus fever, trachoma, infantile paralysis, Rocky Mountain spotted fever and influenza. Congress provides an emergency fund of approximately half a million dollars annually for expenditure by the Public Health Service in threatened or actual epidemics. In order to prevent the spread of leprosy a law of February 3, 1917, provided for the segregation and care of lepers by the Public Health Service. Aside from its humane advantages, the benefits of this provision in the future may be expected to be greater than any single measure now in force for the control of this disease. On account of the danger to the public of the exploitation of contaminated or inert biologic products used in the prevention and cure of diseases of man, Congress enacted a law July 1, 1902, to regulate their propagation and sale in interstate traffic." . . .

"INVESTIGATION OF MATTERS PERTAINING TO THE PUBLIC HEALTH. The conduct of research work is a fundamental function of the Federal Government. Public health research offers the broadest field it may occupy for the improvement of hygiene and sanitation. Nevertheless, Congress long delayed providing the necessary authority and funds for these particular activities, and such investigations as were made were accordingly conducted by officers of the Public Health Service incidental to their regular duty." . . . "For example, a research laboratory was established by the United States Public Health Service at the marine hospital in New York in 1887. It was transferred to Washington in 1891, and ten years later general authorization of law was obtained for investigations of contagious and infectious diseases and matters pertaining to the public health, and a building was provided in which to house the hygienic laboratory of the service. From this laboratory extensive studies have been conducted, but, with a view to the general enlargement of research activities, a law of August 14, 1912, authorized the Public Health Service to study and investigate the diseases of man and conditions influencing the propagation and spread thereof, including sanitation and sewage and the pollution, either directly or indirectly, of the navigable streams and lakes of the United States." . . . "The existence of general law relating to research does not prevent Congress on occasion from enacting special laws prescribing particular investigations. For instance, an Act of August 24, 1912, authorized the United States Public Health Service to make a special investigation into the prevalence of tuberculosis, trachoma, smallpox and other contagious and infectious diseases among the Indians of the country, report, with recommendations, to be made within a specified period." . . .

"PUBLIC HEALTH EDUCATION. Public health data are of use only as they are disseminated and used. For more than fifty years, therefore, the United States Public Health Service has issued weekly the Public Health Reports, embodying abstracts of consular sanitary reports from ports throughout the world and other pertinent information bearing on the public health." . . . "In addition to the weekly *Public Health Reports*, there is authority in law for the publication of scientific articles in bulletins of the hygienic laboratory, and since 1912 a series of publications known as the *Public Health Bulletins* has been issued from time to time. Authority in law also exists for the publication of an annual report, and it is obligatory on the Surgeon-General to submit this report each year to Congress."

PHYSIOLOGY

UNDER THE CHARGE OF

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Capillary Permeability.—EUGENE M. LANDIS (from the Department of Physiology, University of Pennsylvania Medical School). The great transporting medium, the blood stream, is everywhere separated from the tissues it serves by a single layer of endothelial cells which form

the walls of the capillary network. The manner and rate of interchange of substances between blood and tissues depends fundamentally upon the permeability of this capillary wall. The microscopic dimensions of the single capillary make the direct study of permeability exceedingly difficult. The subject has been attacked indirectly, however, by methods such as: (1) The measurement of lymph production, either retained in the tissues as edema fluid or collected from the ducts; (2) the passage of substances which can be identified either by sight, as in the case of dyes, or by chemical analysis; (3) the study of changes in blood volume, indicated by cell counts or hemoglobin determinations. From a study of lymph formation, Starling has concluded that since the capillary wall is normally impermeable to the proteins of the blood, the transfer of water depends primarily upon the balance between capillary blood pressure and the osmotic pressure of the plasma colloids. An excess of ecapillary pressure causes an outflow of fluid, while a reversed relation is accompanied by absorption. The integrity of the capillary wall is of the greatest importance, since impairment of its vitality increases its permeability to proteins with a proportionate reduction in the effective colloid osmotic pressure. In the normal vessel, however, according to Starling, capillary pressure, in association with osmotic factors, determines the direction and amount of fluid passage. More recently Krogh and Harrop (1921) have found that with the dilatation caused by the narcotic urethane in 5 and 25 per cent solution the permeability of the capillary wall increases to such a degree that plasma with its colloids drains off completely, leaving the corpuscles tightly packed together within the vessel. Capillary pressure was not measured in such a region, but is inferred to undergo no change. Krogh concludes that (1922): "No dilatation of capillaries involving mechanical stretching of the endothelium can take place without being accompanied by an increase in the permeability, an increase which runs, on the whole, parallel to the degree of dilatation and which allows all the normal plasma colloids to filter off rapidly when the capillaries are strongly dilated." Comparison of the low pressures in the venous capillaries of the human skin with the colloid osmotic pressure of plasma as determined in collodion sacs of graded permeability led to the further conclusion that there is in almost all tissues an excess of the effective osmotic pressure over capillary blood pressure. Therefore, capillary permeability is believed by Krogh to depend upon the diameter of the vessel, while capillary pressure is considered to be of minor significance. However, in view of the evidence already accumulated in favor of the Starling hypothesis, the action of substances which influence the passage of fluid through the capillary wall should be carefully considered with reference to: (*a*) Possible injury to the endothelium and (*b*) changes in capillary pressure, before ascribing their activity to modification of the endothelium itself. It is the purpose of this paper to summarize the more recent experiments which have shown or suggested the importance of these two factors in changing the normal mechanism of fluid interchange through the capillary wall.

1. *The Effect of Injury on Capillary Permeability.* The striking edema produced by paraphenylenediamin has been shown by Tainter and Hanzlik (1924) to be due to an inflammatory increase in capillary

permeability, which permits the escape into the tissue spaces of whole plasma, including fibrinogen. The gelatinous character of the edema is ascribed to the passage of protein through injured capillary walls. An increased hemoglobin percentage and the accelerated passage of colloidal dyes into the edematous areas indicate an abnormally free outflow of fluid. The development of edema is prevented by a fall in systemic blood pressure or by epinephrin, the latter in spite of an increased systemic blood pressure. Hirschfelder (1924) demonstrated injury to the endothelium by staining with trypan blue, even when edema was prevented by epinephrin. This indicated that epinephrin has no direct protective influence on the capillary endothelium, but acts through its reduction of peripheral pressure. The gradual development of pulmonary edema in the heart-lung preparation is ascribed by Lambert and Gremels (1926) to an injury of the pulmonary capillaries by toxic substances which form slowly in defibrinated blood. They induce the condition more acutely by using blood which has been kept for some hours, and by injection of silver-nitrate solution into the pulmonary artery. Their inference is supported by histologic examination. The endothelium is poorly stained, sometimes entirely absent. Frequently the cells of the capillary walls are granular and without visible nuclei. Pulmonary edema produced by intravenous saline solution, on the contrary, showed little pathology on microscopic examination. They suggest that the development of pulmonary edema in man may be partially due to the production of injurious substances by the chronic anoxemia which precedes the condition. It is of interest in this connection to note that Loeb, Atchley and Palmer (1922) found that serous effusions in cardiac cases have a relatively high protein percentage. Uncomplicated hepatic cirrhosis and nephritis produce fluids with 0.6 to 0.9 per cent protein. In cardiorenal and cardiac cases the protein was increased to 3.3 to 4.5 per cent, while in a true inflammatory condition, tuberculous pleurisy, the fluid contained 5.6 per cent. The transudates contain an excess of chlorids over that in the blood serum, such as would be expected if the two fluids were separated by a membrane relatively impermeable to proteins. The difference in the chlorides becomes less evident as the protein content of the transudate approaches that of the serum. Dialysis of the serum in collodion sacs against the transudate caused only slight changes in salt concentration, which indicated that the relations depend upon a simple membrane equilibrium and are not due to properties peculiar to living protoplasm. Lewis (1924) and Lewis and Grant (1924), in a study of the factors influencing the formation of wheals in urticaria factitia, find that this type of edema is independent of the increased permeability of vessel walls which might be ascribed to distention, and is only aided by increasing the filtration pressure. It is is apparently due chiefly to a heightened permeability of the vessel wall, though the rapidity of the edema formation depends upon the rate at which blood is supplied to the damaged vessels. Tissue injury is believed to liberate a substance, possibly of the nature of histamin, which is responsible for the reactions observed. The effects of injury upon permeability have also been emphasized by Osato (1922). Nontoxic colloids, such as homologous immune sera, pass very slowly from the blood stream into the lymph and have practically no lympha-

gogue action. Toxic colloids, however, such as foreign proteins or heterologous immune sera pass rapidly from the blood into the lymph, at the same time increasing markedly the volume of lymph. The difference is attributable to an increased permeability of the endothelium for colloids incident to injury by the toxic substance. The action of formaldehyde, applied externally, upon the circulation of the frog web has been studied by Jacobj (1923). After a preliminary period of moderate dilatation and increased flow there follows a marked concentration of red cells and finally stasis, due to the loss of plasma through the endothelium with the formation of solid masses of corpuscles within the capillaries. The sequence described resembles closely that given by Krogh (1922) for the action of urethane. By Jacobj, however, the effects are considered to be due wholly to injury of the capillary wall, which is indicated by the very wide dilatation, by the abnormally increased permeability and by the apparent stickiness of the endothelium and erythrocytes. Herzog (1925) has verified Krogh's experiments and conclusions by observing capillary circulation in the frog's tongue, after injecting intravenously a mixture of Chicago blue and India ink. Pinching the tongue with forceps, the application of hot water (45° to 55° C.) and 20 per cent urethane—all produce stasis, with dilatation, loss of plasma, increased passage of the dye and also the adherence of ink particles to the endothelium. The dilated capillary is believed by Herzog to be not only more permeable but also more sticky than the constricted vessel. Both effects are best observed in the areas of stasis where, however, there is a definite tendency toward irreversibility. Though the possibility of injury is considered, he concludes that the increased permeability and stickiness are both due to dilatation, in support of Krogh's views. It seems evident that the effects of injury to the endothelium are uniformly in the direction of greater permeability of the capillary wall, not only for water but also for the colloids of the plasma. On this account, in the study of the normal mechanism of fluid interchange it is highly important to rule out any possibility of injury. The work of Hirschfelder (1924) and of Tainter and Hanzlik (1924) indicates in addition that the manifestation of this increased permeability, in the form of edema, depends to a certain extent upon an adequate capillary blood pressure.

2. *The Influence of Capillary Blood Pressure on Fluid Interchange.* The accurate measurement of capillary pressure has an important bearing on the determination of the mechanism of capillary permeability. A relatively close relation between capillary blood pressure and the osmotic pressure of the plasma proteins would be in favor of the Starling hypothesis, particularly if there is a measurable gradient of pressure fall between the arteriolar and the venous capillary. The determination of capillary pressures by direct manometric measurement is the only method relatively free from technical objection. The first of such direct measurements were made by Carrier and Rehberg (1923), who introduced fine glass tubes, connected to a manometer into the superficial venous capillaries of the human skin. They found very low values, the minimum level lying between 4.5 and 7 cm. of water. Measurements restricted to a single location, such as the venous ends of the capillary loops, however, could not yield information concerning a pressure gradient through the capillary net. A series of determina-

tions (Landis, 1926) taken at various points between artery and vein in the mesenteric circulation of the frog indicates the presence of such a gradient. Thus the average pressure in the arteriolar capillary was found to be 14.5 cm. water and in the venous capillary only 10.1 cm. White (1924) has placed the osmotic pressure of the plasma proteins in the frog between 10 and 12 cm. water. This relation is sufficiently close to indicate the probable importance of capillary pressure in determining the direction and amount of fluid passage through the endothelium. Direct measurement has also shown that there is a measurable rise in capillary pressure accompanying the dilatation and increased flow produced either spontaneously, by very dilute urethane (1 per cent), or by application of warm saline. This would explain any moderate increase in the outflow of fluid which might be observed when capillaries become dilated. Okuneff (1924) has found that local heating of the skin, thereby producing a peripheral dilatation and a more rapid flow, increases the passage of dye from the blood stream into the heated tissues as compared to other areas. The effect was more marked with prolonged heating. Anitschkov (1924), in reviewing the mechanism of the passage of colloidal dyes through the endothelium, concludes that any active hyperemia, or any condition such as heat, causing a local vascular dilatation, increases the passage of dye through the endothelium. Both authors mention the possibility that application of heat may by this mechanism influence the localization of harmful substances circulating in the blood. Hirschfelder (1924) emphasizes the circulatory factors in the production of edema by the application of mustard oil to the conjunctiva of the rabbit. Epinephrin inhibits the development of edema on the treated side for about two hours, at which time the vasoconstriction due to the drug disappears. The behavior of dyes in staining the capillary walls indicates that the endothelium has not been protected by any direct effect of the epinephrin, but that the lessened edema is due to a diminution of filtration pressure. Vasodilatation increases the edema only when it also raises capillary pressure. Thus sodium nitrite locally increases the inflammatory effect of mustard oil, but intravenous injection so lowers systemic pressure that it is insufficient to produce the edema. Cocain, because of its peripheral constrictor action, acts like epinephrin. The importance of capillary pressure is noted also by Tainter and Hanzlik (1924) in their study of paraphenylenediamin edema. Loss of fluid could be prevented by a marked fall in systemic blood pressure, and also by the administration of epinephrin, which markedly increases general pressure. Both procedures probably have the same effect on capillary pressure. Petersen, *et al.* (1923) found that epinephrin causes chiefly a diminution in the quantity and protein content of the lymph flow, and attribute its action to an "inhibition" of the endothelium. Anaphylactic shock, on the other hand, increased both volume flow and protein content. They regard the endothelium as a specialized tissue which when stimulated is highly permeable, when resting less so and when injured completely permeable. Injection of pituitrin, which resembles epinephrin in its effect on vascular tonus, has been shown by Bayley, Davis, Whitman and Scott (1925) to diminish the volume of lymph collected from the thoracic duct, and to delay the exit of physiologic salt solution from the blood stream. They attribute the result to direct action of pituitrin on the endothelium. Lee (1925) has found

that histamin produces a marked fall in cerebrospinal pressure coincidently with the lowering of arterial and venous pressure. Microscopic observation through a window in the skull provided evidence of dehydration of the brain substance. Though recognizing that the effects are complicated by circulatory factors, he postulates the functional difference of the cerebral capillaries and advocates the consideration of an active participation of the endothelial cells in explaining the phenomena of capillary permeability. Definite proof of the quantitative action of capillary pressure as distinct from systemic blood pressure on the passage of fluid through the endothelium is lacking. But there is sufficient indication of its importance as a factor in both normal and injured vessels to demand that it be measured in any problem concerned with capillary permeability. The accumulation of such data will be of the greatest value in determining the mechanism of the transfer of water and dissolved substances through the capillary wall.

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